less frequently.

In the next slide indicated Western Blot data of monkey plasma in which the experiment was done to detect any antibodies that were present in monkey plasma by incubating them with strips of nitrocellulose that contained Foamy Virus antigen from infected cell lysate. Number 1 in each case indicates the day of the blood transfer, and Number 2 indicates 48 months post-transfusion. This is the profile that is seen for the donor animal. These bands are specific for Foamy Virus infection because they're antibody-specific bands for Foamy.

In the case of one of the recipients, Recipient 1, this is the sample from the day of blood transfusion, and this is 48 months post-transfusion, and you can see Foamy-specific antibodies that have already developed -- that actually developed much earlier and you can see persistence of these antibodies at 48 months post-transfusion. Similarly, in the second recipient animal, we also can see Foamy-specific antibodies developed and persisting for 48 months.

In the negative control animal, you can see that there are background bands that were present on the day of blood transfusion as well as the same

level persisting even at 48 months post-transfusion. There was no difference in terms of increased levels, and I should mention when these are lined up side by side none of these bands correspond to any of the bands here. Even these two bands are in between the two virus-specific bands.

In the next slide, I'll describe to you the studies that we conducted to demonstrate that infectious virus can be isolated from the blood-transfused animals. Monkey PBMCs were cold-cultured with a highly susceptible cell line that we had found in our lab -- Mus dunni cells. We have found several years ago that Mus dunni cells, which is a wild mouse cell line, is a fibroblast cell line, was highly sensitive to Foamy virus detection, so we used that in our lab.

And the control was Mus dunni without PBMCs, and this was set up as a negative control that is critical for the reverse transcriptor assay that is used to determine virus production in the assay. And then filtered supernatant was collected at each cell passage every three to four days for testing of the reverse transcriptor assay for virus production. And if a culture was negative, we would continue the culturing for up to 30 days. Otherwise, if there was

cytopathic effects seen, then we would terminate the culture when the culture had greater than 75 percent cell destruction.

The PBMC samples that were analyzed in the assay were from the transfused monkeys, both of the recipients, R-1 and R-2. We also used the donor monkey to demonstrate virus isolation from the day of blood transfer, and the negative control monkey was used as a control sample.

In the next slide are shown the results from the virus isolation study. Basically, these are the days in culture and up here is the RT activity, which indicates the amount of -- which correlates with the amount of virus that's released into the medium. So the Mus dunni cells without any PBMCs are shown in the blue triangle in all of the four panels, and this is the background activity. From the donor animal, we found that the virus was detected after ten days of cold culture. And, as you can see, it increased -- virus production increased rapidly once CPE started, and then the culture was terminated about day 18 here. And this is high virus production with high CPE here.

In the negative control animal, which is in the diamond red here, these are cells obtained from the animal at 22 weeks post-blood transfusion. Of

course this animal did not receive any blood, but this is the time point that we used for the blood transfusion animals. And here at this time point the PBMCs from the negative control animal did not release any virus and the animal was clean.

From both the recipient animals, R-1 and R-2, virus could be isolated from the PBMCs of the 22-week sample in both cases. However, there was no virus released from the day of blood transfer that is shown here in the squares in both cases, and that ran along the same levels as the negative Mus dunni cell control.

The next slide, these results that I've presented to you indicate that Simian Foamy Virus was transmitted by whole blood transfusion and established a persistent virus infection in naive monkeys. This was demonstrated by the detection of virus-specific antibodies, by nucleotide sequence analysis as well as by virus isolation. I should mention to you that the nucleotide sequence analysis that we did was for a limited region in a part of the viral genome, and in that region the sequences that were present in the transfused animals was identical to that in the donor animal.

And I also wanted to mention that in this

study we used one donor, and we had infection in both of the recipients. In another study that is still in progress, we used a different donor whose Foamy Virus has distinct biological properties from this particular donor virus. And in that case, as of right now, we do not have evidence of blood transfer of the virus. So this sort of I think emphasizes the fact that the transmission can occur but it might be affected by other factors including the virus properties itself or other properties of the host.

In the next slide, this is my acknowledgement slide. I just want to acknowledge Tanya Kramar, who has done a tremendous effort in generating the data for the study, as well as the wonderful Sieber Veterinary staff and also to thank Jay Epstein and Ed Tabor and Yura Nakase for their consultation during the studies. Thank you.

ACTING CHAIRMAN ALLEN: Thank you, Dr. Khan. Dr. Strong?

DR. STRONG: Did you also monitor clinical symptomology? Are there any symptoms, blood chemistries, et cetera?

DR. KHAN: Yes. I'm sorry I didn't mention that. Basically, in terms of -- there is no overt symptomology in the animals. They were examined

regularly by physical exam and fever and all of the physical parameters. In terms of the clinical reports, I have not yet completely analyzed all of them, but as of right now there does not seem to be anything that sticks out as something being abnormal. But I do have all of the results longitudinally for the entire year, so we will look at each of the parameters on the long list of different values and then see if we see anything developing over time. But there's nothing overt that we can see.

DR. STRONG: I think it was on one of your slides you found the virus in neural tissue. Can you say something about that?

DR. KHAN: That was from published data in terms of the neural cells. There's a report by Ruccio et al. in which they have shown that a variety of different cells and tissue culture, including the neural cells, can be infected with the virus. But also, actually, virus has been isolated from the brain of monkeys, so in 91 primates it seems that the virus is distributed throughout the entire animal in terms of the viral DNA sequences. Now, in terms of the actual expression of infectious virus, that seems more limited.

ACTING CHAIRMAN ALLEN: Other questions?

When it takes so long to do such a study, it obviously is not a very happy question to ask but are you now going to go back and look at individual components, i.e. peripheral blood monocytes separated and washed, packed red cells and washed packed red cells and plasma?

DR. KHAN: Actually, the way I'm thinking about addressing that -- of course it's a scientific curiosity as well as a public health question. What we are setting up to do is we will be evaluating these cells over time that we have collected from the animals. We have frozen down and preserved PBMCs and we will see which cells are infected at what time post-transfusion so we can get a handle what population of cells are infected or are they all infected? And we will be conducting some additional studies in which we can get fresh samples and we can see which component might be infected in fresh samples.

In terms of -- I think once we have an answer as to what cell types are infected, then I think we can see whether we need to do any more transfer studies.

MR. NAKASE: Arifa, thank you very much for a nice talk. This is Yura Nakase, FDA. You said

what's the timeline for developing the antibodies and, as you said, that takes by week 20 you see the virus coming out, at least in the cell culture. When do you see the antibodies developing and if they are -- and I read in the literature there are neutralizing antibodies that can suppress the virus -- what's the timing in these animal experiments when you see antibodies and when you see the virus?

DR. KHAN: Right. We have that data and I did not sort of include all of those tables. In terms of the neutralizing antibodies, we're currently looking at the presence of neutralizing antibodies and the titers in these animals and in the parent animal. So far we don't have data on development of neutralizing antibodies with time, but we just have data with developing whole antibodies in Dot Blot assay. I'm struggling to recall the table. I think the PCR result is earlier than antibody development, and I will have to go back and check it.

ACTING CHAIRMAN ALLEN: Other questions or comments? Yes, Dr. Lew?

DR. LEW: Just to look at the issue for while I'm wondering if it's pathogenic, are there any studies that are going to aggressively look for this, like in immunocompromised animals, although just the

thought of seeing the slide on the HIV with the Foamy Virus it's quite possible that having them together would make HIV less pathogenic. I mean who knows, but I mean --

DR. KHAN: It can go either way, you're absolutely right. And I think those are studies that need to be done formally. I think there is heresy but I don't think it's been done rigorously. Actually, we have samples in the lab which we have obtained from other projects that I've been doing in my lab related to SIV and AIDS in monkeys, and we have some animals that were Foamy-negative and some that are positive, so we can go back and look at that question now to see what is the relationship of the two viruses in terms of expression over time -- or replication, I should say.

DR. SANDSTROM: Paul Sandstrom, Public Health Agency of Canada. Just on the issue around HIV or lenti viruses and Foamy Virus, there is a recent publication that came out in Journal Virology, I think it was, what, two weeks ago, that showed that -- it was an in-vitro system so it was done in cell culture, but that the presence of persistent infection by SFV increased the -- it wasn't infectivity but it was actually the binding of lenti viruses to cells. It

was probably through Heparin celfate profile proteoglycin pathways but implying that there might have some effect -- that Foamy Virus infection might have some effect on, I guess, the ability of envelope viruses to infect cells.

DR. KHAN: I mean I think it's fortunate that the two viruses are fairly different genetically, because in cases where the viruses are related, of course there's recombination and that would be an additional concern. So I think these are situations that need to be further studied in the co-infection. Nick?

MR. LERKER: Nick Lerker from UC Davis. Just a comment on an observation we've made on that last question. In the SIV macaque model for AIDS, we have the so-called fast progressors. There's different courses of infection in these animals. And one of the questions we wanted to know is could it be possible that Foamy Virus might be associated -- or co-infection with Foamy Virus associated with these fast-progressing cases. So we retrospectively looked at fast progressors and non-fast progressors for their Foamy Virus status, and in the retrospective study we did not find any significant difference in terms of their SIV clinical course related to the Foamy Virus

status. So it did not seem to be a co-factor in the common sense of that.

DR. KHAN: So, Nick, may I just ask you, did you look at the levels of virus replication in the study or how did you --

MR. LERKER: This was a rather crude retrospective study just looking at -- it was animals that had been identified as fast progressors.

DR. KHAN: Oh, okay.

MR. LERKER: We then went back and looked at their stored archive serum for Foamy Virus status, and so we did not look at virus loads. That would be need to be done as well.

ACTING CHAIRMAN ALLEN: Thank you. Other questions for Dr. Kahn? Okay. We'll move on. Our next two presentations are from colleagues at Health Canada, recent research results, Dr. James Brooks. Welcome.

DR. BROOKS: So I'd like to thank people on the Blood Products Advisory Committee for inviting me to present to you the data I will today. I'm James Brooks, and I work at the National HIV and Retrovirology Laboratories, which is actually -- now there's been a new agency created, so now we're actually part of the Public Health Agency of Canada.

And under my other hat, I'm a clinician, I'm an infectious disease doctor, and so I'm also under the auspices of the University of Ottawa in the Division of Infectious Diseases. So I'm here today, and I'm going to talk to you about Simian Foamy Virus transmission through blood transfusion. Next slide, please.

It's been well covered before but I'm just going to briefly go over Simian Foamy Virus infection in humans just to highlight a couple of points just from my perspective, but I certainly won't go over things exhaustively, as it's been well covered by my colleagues. And I'll talk a little bit about the Canadian expanse with Simian Foamy Virus because I think it's pertinent for two reasons: One is the demographics of the exposure of people who work with non-human primates, and also to highlight some of the unique factors about Foamy Virus infection that we think are relevant. And then I'll go on to talk about the results of our blood transfusion study. Next slide, please.

So as has been described before, that all the human retroviruses that are known to have originated from non-human primates, there's ongoing transmission with other Simian retroviruses, such as

SFV, SIV and SRV. We think that SFV is important because it's probably the most easily transmitted of the Simian retroviruses. And the second point is we have good assays to follow this. But our perspective is that this is just a marker of sites where retroviral transmission can occur. Next slide, please.

As has been described previously so well by Walid, these are the S Foamy Virus infections in humans or publications describing Foamy Virus infections in humans that have been published. And this is both in the occupational setting and most recently with the paper by Nathan Wolfe. I just want to point out here that one of the papers that we put out on cross-species retroviral transmission from macaques to humans was important because the most popular animal that is used by medical research is either a cynomolgus or the rhesus macaque and we've shown that there was an infection that did originate out of macaques and was transmitted to humans. Next slide, please.

I'll talk a little bit about what the climate is of exposure to non-human primates in the occupational setting, at least in our experience. Next slide, please.

This graph represents the monkeys or non-human primates in general who are registered with the Canadian Council on Animal Care, which is an organization that facilitates accreditation for people involved in non-human primate research. And as you can see, as I have more recent data that's not in this slide, that there's around 2,000 non-human primates a year that are registered in Canada for experimental purposes. And the thing to bear in mind is that each one of these animals is going to be looked after by a number of people, including people who clean the cages out, the people that mobilize them for experiments, the veterinarians who are involved and also the laboratory workers who are going to be involved in analyzing the samples. And as you can see, it was mentioned that most of these animals are either cynomolgus or rhesus macaques. Next slide, please.

When you try and identify the low side where people are exposed to non-human primates, it's difficult information because people are reluctant to divulge that they're involved in work with non-human primates. What I am able to find out is that there are 21 institutions that are registered with the Canadian Council of Animal Care in Canada as being involved in caring for non-human primates. When you

look at a larger scale and you look at an industry-sponsored organization that is interested in promoting the welfare the animals in zoos and aquariums, there's another 28 institutions there that are registered, but not all of those would have non-human primates. And if you take the perspective of looking at any institution that's involved in having animals for display purposes in Canada, there's more than 100 institutions in Canada. Next slide, please.

And this is just to show you the relevant data from the United States, and this was kindly provided by Tom Damercus at the Division of Quarantine. As you can see, again the predominant animals that are imported into the United States are both cynomolgus and rhesus macaques, and the numbers again more recent data shows it's somewhere between 10,000 and 15,000. This is just to give you some perspective on the exposure. Next slide, please.

And then this I'm just going to mention this very briefly and what our experience was with human Foamy Virus infection in the occupational setting. And it's important too for the understanding of what the levels were of exposure and again for the macaque infection. Next slide, please.

As you can see, the burden of exposure is

very high and you can see that of the people that were in the study more than 90 percent were exposed to some of the fluids. In terms of the intensity of exposure individually, bites were present in about three-quarters of the people who were involved in the study, and things such as needle sticks were still present in about half of the people in the study. Next slide, please.

And what we found was that there were about two out of 46 -- well, there were exactly two out of 46 participants who were Foamy Virus-positive, and this represented about four percent of the study population, which is consistent with other studies. But, importantly, the infection, at least for the one that we were able to have molecular data on, originated out of a macaque. Next slide.

If we were to ask the question are we able to define the risk based on the pattern of exposure, the answer was, no, the demographics of the infected and uninfected were the same, and if you look at the patterns of exposure between the infected and the uninfected, they were exactly the same. When we looked from the perspective of what potential risk that it exposed the blood supply to, we found that about half of the people had donated blood and the

question was phrased, "ever," so it's not necessarily regular blood donors. From the perspective in Canada, the regular blood donation occurs in less than five percent of the population. So this group would be overrepresented, and it's probably due to the part that because of their work in a biomedical institution, there's on-site recruitment for a blood donation. So they would be frequently participating. Next slide, please.

And I won't go through this in detail because again it's been covered by Walid, but this is sort of the segue of where we launched into the study of the blood donation.

I just will highlight one point about -- these are the paraphrasing of the questions that were put out by BPAC at the last meeting, and that is: does foamy virus cause disease in humans?

And really one of the things that I think Walid brought up very well is the selection bias, so that if somebody is unwell or is deceased, they would not be captured by these studies that have been done here in an occupational setting.

And then finally this is where we move forward, and Walid has already discussed the study here by Dr. Boneva and the limited information that is

currently available.

Next slide, please.

So the study design was very similar to Arifa's and it's simple in conception in that we took blood from a foamy virus positive donor and transfused it into a negative recipient, and then what we did was did a sham transfusion with saline into a negative monkey and followed the out over time, carefully keeping them in a segregated and foamy free environment so that we could be sure that if we did document evidence of transfusion or -- sorry -- evidence of infection in the negative monkey, it was the result of the transfusion.

Next slide, please.

We did some baseline work, and we were able to establish that the donor and recipient had O type blood. The blood grouping in monkey is quite complicated, but at least at this level we're comfortable that we're compatible.

We also took white cells, lymphocytes out of the donor animal and were able to show in tissue culture that they produced infectious virus. So that there was virus there that would be potentially infectious to the recipient.

And then we also were able to show that if

we took the virus from the donor monkey it was able to infect the white cells from the recipient monkey. So there was no a priori reason why the monkey that we had found that was foamy virus negative could not get infected with the foamy virus.

Next slide, please.

This was our protocol in that we quarantined the monkeys at minus 12 weeks, but in fact, we had data going back that they were either foamy virus positive or foamy virus negative, respectively, for about two years before then, but this was when they were sort of enrolled in putting the strict segregation.

And then at time zero -- and the lines here represent sample drawings -- for the transfusion we used ten percent blood volume of the recipient monkey meant to approximate about 500 mLs of blood in a human, and it was citrated blood, and it was a direct transfusion.

And then the other thing he did was he harvested a lymph node at around the 16 week time point.

Next slide, please.

So these are the results that we were able to obtain. This is a Western Blot with a combination

of different foamy virus antigens that are present, and it's an assay that's being well described and published by others and us, and so this is the pattern that you would see with the donor monkey with the gag doublet here.

And here is the recipient that you can see at minus 12 weeks and zero, at time zero. It's clearly negative. This is interesting because what you see here is you see a conferring of passive immunity in the immunoglobulins that went across from the donor monkey, and you can see that the pattern here wanes at four weeks, and so they're negative at eight weeks.

And then by nine weeks trust me. It's there. There is a gag doublet here, and I'm happy to show data to anybody who would look, but by 12 weeks you're seeing that gag doublet, and the strong evidence at that point is seroconversion in the recipient monkey, and if you look at the placebo monkey, you can see that they're clean throughout that experiment.

Next slide, please.

When we asked the question can we find evidence of the actual virus using published PCR primers in a nested reaction, the answer is yes, and

the time points correspond here. Again, if you look at the donor monkey, you'll see the bend here is characteristics, 464 bases. We have sequenced this particular piece of DNA. So we know it is foamy virus.

And then if you look here again at minus 12 weeks, zero, one, two are negative, and then here at about the eight week mark there, you see that there is a strong signal, again, at nine, 12, it remains the same. If you look at the placebo monkey, they're negative.

The next slide, please.

And I know there's been some questions about this, and this is -- Harriet Mertks and the technician in my lab developed this real time PCR assay, and what we were able to do is to get a pro viral load on DNA extracted from whole blood, and so these are copies per thousand cells, and this is total cells in the DNA extracted from the blood.

And as you can see, this is the donor, has viral load, and it ranges here between five and ten, and this is the placebo. As you can see, it remained at zero throughout the course of the experiment.

The recipient monkey here. This is right at the threshold of detection. So depending on how

many replicates you can do, it can pop up at a very, very low level at six weeks here, and then it's a strong signal here at eight weeks, and it goes to quite a high level here to somewhere over 40 copies per thousand cells and then decreases to what we would predict to be the set point here, and this is around four copies per thousand cells.

Next slide, please.

We also did some preliminary immunological analysis in this experiment, and you know, I'm going to say it's preliminary just because the sample size here is one. So it has to be interpreted with caution.

What you see in both the recipient and placebo monkey is there's a decrease in the total lymphocyte count, and when I discussed this with the veterinarian who was involved in the study, he says it's not inconsistent with the animals being housed singly. He said that in terms of the cynomolgus macaque monkeys that were used in the experiment, one of the most stressful things that can happen to them is to be taken out of the group setting.

So he says this is not unexpected, and once we determined that the animal had become foamy virus positive, we would relax the housing

requirements, and with the negative placebo monkeys return back to the negative colony, and so you can see that once that pressure was off, then they came back to baseline.

Next slide, please.

If we look at the CD4/CD8 ratio in both the recipient and the placebo, the placebo monkey here is just showing some gradual variation, but really, you know, you could draw a line through there and it looks about the same.

When we looked at the recipient monkey in terms of what happened to this ratio of cells, you can see that this is the time of transfusion here, that something happens, that there's a decrease here in the ratio to .8, and then there's a doubling here, an inversion, as it were, up to 1.6 from the ratio, and then it comes back to around baseline.

So as you can see, this could be either -- because it's a reciprocal relationship, it can either be the CD4 going up or the CD8 going down.

Next slide.

So when we went back and when we just looked at the data more carefully to try and figure out what was going on, the pattern that we're seeing here, and this is in the recipient monkey is that you

see that the CD4 count dropped initially after transfusion here, and then by a delay there probably around two weeks, then there was a fall in the CD8 count, and that called an inversion of the ratios, and then over time they both come back to baseline.

Next slide, please.

So from this small study and the preliminary data that we've been able to accumulate, what we feel we've been able to establish is that simian foamy virus is transmissible by whole blood transfusion in the native host.

The second point is that there's an apparent immunologic disturbance after the transfusion. This could be for any number of reasons. It could be related to the transfusion alone. It could be related to foamy virus transmission. It could be related to some other virus that is transmitted, and because it's only one monkey that died, I would urge you to interpret that with caution.

Then there wasn't a good way to present this, but I will tell you because it's related to the new information that there is a replication competent foamy virus present at distal sites, and in this experiment when we took the lymph node, we removed some of the lymphocytes and isolated them and put them

in tissue culture and stimulated them, then extracted RNA, treated them with RNAs for DNAs, and then looked to find out whether we could detect evidence of replicating virus with RTPCR, and the answer to the question was, yes, we could at that level.

And next slide, please.

And so this is meant to address some of the obvious questions that will come out of this, plus some caveats, and that is which blood components transmit foamy virus and will there be any inactivation steps that will prevent transmission of the foamy virus.

And then what about people who have captured previously kept monkeys and pets?

So I'll just deal with the first two points and then just give some perspective on the last point.

Next slide, please.

Well, in order to show transmissibility of foamy virus through blood transfusion, we only required two monkeys. So that's it. It's a relatively easy experiment, but to demonstrate non-transmissibility is much more difficult. I'm not a mathematician or an epidemiologist, but from what I've been able to ascertain is that in order to show non-

transmissibility at a five percent level, even if you had 30 monkeys, the confidence intervals at that would still be ten percent. So it's difficult to show absolutely there's no transmission.

And this is obviously made more difficult by the context of relatively few foamy virus free monkeys being available.

Next slide, please.

And from the perspective of pet ownership of non-human primates, and this is the only data that I could find that comes from the United States, and there was no Canadian data that I could find. Importation of non-human primates as pets was banned in 1972, but before that, in these two years there were more than 200,000 non-human primates imported as pets.

I'm going to point out here that these are new world primates, okay, and there hasn't been an established -- it hasn't been established that there is a transmission of foamy virus from new world primates into humans, and there are no known serological assays to detect for this infection, but this is just meant to place it into some context.

And the next slide, please.

So these are the people that I'd like to

thank, and these are the people that work with me or I work for. There's Harriet Mertks, who does all of the work and did all of these experiments and did a great job on them. She keeps all of the data and keeps me organized.

And Paul Sandstrom who is my boss, who has been very supportive here.

And Frank Buffer who is our boss, very supportive.

But over at the Health Products and Food Branch, there's Jocelin Fornier (phonetic), and he's the veterinarian that's been instrumental in getting this study going.

There's Peter Ganz who has been very supportive from the perspective of the blood regulators.

And Dr. Rouimiana Boneva, who was very helpful in terms of setting up this study in the beginning, and also to the people who support me as a clinician-scientist in the Division of Infectious Diseases in the Department of Medicine, University of Ottawa.

Next slide.

I'm just going to leave you with this slide because I think it's important for a perspective

because what it reminds me to tell you is that while we were able to look for foamy virus transmission in areas where it may seem likely, there are other situations where it may be occurring that we have no idea, and it's only a matter of where we shine the light.

So this is Jane Goodal. This is from a national newspaper, but as you can see, in sort of settings, risk prolonged exposure to non-human primates. You might expect transmission to occur there, but this photograph there, and I got this from somebody I know, this is her mother, and this is back probably in the late '40s this photograph was taken, and here I think this is a macaque she's got. So it's unknown how many people would be like this around.

And here what you have is you have a monkey here and a cat who are eating out of the same bowl, and both of these animals are potentially foamy virus infected with respect to the thing, and there has been evidence in the past of transmission of retroviruses between felines and non-human primates. So here you're having this crucible that has been created that we may not be aware of, and this may be unknowable.

Anyway, thank you for your time.

ACTING CHAIRMAN ALLEN: Thank you.

That photograph of Jane Goodal reminds me of a report I saw after the epidemic of monkeypox that we had here in the United States, what a year or two ago, transmitted by prairie dogs or that was the prairie dogs with the vector, and there was more than one picture of humans kissing their prairie dogs with the explanation, "They're so cute." So transmission does occur.

Questions for Dr. Brooks? Dr. Strong.

DR. STRONG: Since you brought that one up, I was very impressed with the high rate of donation amongst people who were infected with SFV. So I wonder if we should be infecting the population to increase our blood donations.

DR. BROOKS: Let me just clarify. Those were people who were involved in the study. So that was total people involved in the study, both infected and uninfected.

Still 50 percent is still ten times better than we do elsewhere.

ACTING CHAIRMAN ALLEN: Dr. Klein.

DR. KLEIN: Of the 2,000 inoculated primates a year that are for medical research in Canada, are a large percentage of those imported or

are they bred?

DR. BROOKS: I won't be able to provide you with absolute numbers on this. There are imported ones, but there are also ones that are bred. But the answer is both, and the numbers for the United States that I got from Tom DeMarcus, that's purely imports.

ACTING CHAIRMAN ALLEN: Dr. Tabor.

DR. TABOR: Thanks again for coming down South to present your data. It has been very helpful, and I know between your studies and Dr. Khan's studies, it really places the SFV discussion in a completely different light than if we didn't have these studies.

And that's true even though there are only small numbers of animals in each of these studies, and in that connection I'd just like to say in response to your statement about how hard it is to do non-transmission studies in the future, this is a problem that we encounter in a number of settings with agents that are only transmissible to rare animals or animals that are very hard to obtain for one reason or another, and I'd like to at least suggest that even though it may not meet statistical requirements, the non-transmission studies in small numbers of animals can be done as long as you have suitable isolation,

suitable challenge studies after the incubation period has passed.

And, again, even though it may not meet statistical criteria, it can be scientifically compelling.

DR. BROOKS: I think that's a fair comment. I agree with that.

DR. KUEHNERT: I just wanted to ask. This question was asked before by another presenter, but just about the issue about the presence of virus in cells versus freely evident in plasma, and you have the pro virus test you did. I'm not that familiar with it. Maybe you could explain that a little bit and whether all of the virus you saw was cell associated or whether you saw any in plasma.

DR. BROOKS: So to answer the question is that the provirus would represent integrated virus. In terms of foamy virus, some of it may be free virus which you're able to catch. The assay that we do is a commercially available standard methodology for extraction of total nucleic acid from whole blood.

Foamy virus, different from some other retroviruses, it's reverse transcriptions that happens early on so that a lot of the virus is already in its DNA form. So it may be technically free at that time,

and it may be captured.

So my feeling is that the predominant virus that we're capturing is truly pro virus. That being said, the predominant virus we're capturing is pro virus that's integrated into the cells. Okay?

I think it's an excellent point you raise about presence of free virus in the plasma, and that is an ongoing part of our study. So we have those samples, and we're determining the best way of extracting them in order to answer your exact question.

DR. KUEHNERT: Thanks.

ACTING CHAIRMAN ALLEN: Yes.

DR. SAYERS: Will you take a question from the floor?

DR. BROOKS: Certainly.

DR. SAYERS: Thanks.

Merlin Sayers.

That one illustration that you showed changing CD4/CD8 ratios, revealing that the transfused monkey's immune response was not the same as the same as the control animal, do you think that might have been a different observation if the control animal had received uninfected blood rather than saline as its control?

DR. BROOKS: I think that's an excellent point you raise, and if I didn't mention it, I meant to mention it, that there are a number of possibilities that could explain that response. One, it could be just chance.

Another response, it could be related to just the transfusion in itself and have nothing to do with foamy virus. It may be as a result of foamy virus being present in the transfusion or it may be because of some other virus that we transmitted along with the foamy virus.

And so you make a valid point.

ACTING CHAIRMAN ALLEN: Other questions?

(No response.)

ACTING CHAIRMAN ALLEN: Okay. Thank you very much.

Our next speaker is Dr. Peter Ganz, regulatory considerations, the Center for Biologics' evaluation, Health Canada.

DR. GANZ: Good afternoon, and again, I'd like to thank the Advisory Committee and colleagues at FDA and CBER for an opportunity to talk a little bit about a snapshot in thinking at least of some of the regulatory issues surrounding simian foamy virus.

Next slide, please.

I'd like to focus primarily on some of the risk management considerations for prevention of transmission through blood.

Next slide.

As James indicated, this isn't a new issue, simian foamy virus certainly for Canada. We've had some discussions around simian foamy virus sine Dr. Sandstrom's and Dr. Brooks' earlier studies, and some of the data in the literature since 2001.

Next slide.

I wanted to show this slide primarily to indicate that although we're talking about simian foamy virus in the context of the blood system, there are, I think, broader public health issues that need to be addressed around simian foamy virus as well.

Next slide.

And, again, I think that certainly within our board federal government mandate in Canada, prevention of and managing the risks of the introduction of new adventitious agents into the human population is really a primary concern.

Next slide.

Just a couple of slides on the context, at least, from my regulatory perspective. Almost 300 different viruses, rickettsia viruses, rickettsia

bacteria, fungi, protozoa. In helminth parasites are known to infect humans as zoonoses.

Many zoonotic infections do not spread further than the index patient, and many do not cause significant disease, except in compromised hosts.

Next slide.

Risks to the public at large are magnified obviously if the are vertical or horizontal transmission of an agent, and also certainly there is a further high risk of exposure in the population if there's transmission through transfusion and transplantation.

Next slide.

What are some of our general risk considerations with regard to simian foamy virus? Certainly there are three points to be considered with regard to virulence of pathogens such as simian foamy virus: time in dose of infection; the immune status and genetic variation of the host and the pathogen, and we heard a little bit about that in earlier presentations.

Some of the specific issues of concern are related to a well adapted host and parasite relationships which tend toward increasing virulence of the pathogen if we look back at other kinds of host

pathogen examples, and also increasing incidence of immune compromised individuals in the general population, I think, is an issue as well.

Next slide.

Although at present we don't have an algorithm to say that if there's an infectious agent identified that this is the particular path we need to follow in terms of protecting the blood supply. Some of the consideration certainly that apply in our thinking are, you know, can the virus infect human cells, and we've seen data presented earlier that, yes, indeed, simian foamy virus does infect human cells.

Can the virus replicate and produce cell free infectious virus?, and again, there's data that says that that's true for simian foamy virus.

With respect to cell types that are targeted, again, the literature and in presentations today, it's pretty clear that the simian foamy virus has a very broad trophism, VNT lymphocytes, macrophage, fibroblasts, endothelial cells, kidney cells, and so forth.

Next slide.

Is the virus cytopathic or temperigenic in human cells? For simian foamy virus we heard Dr. Khan

and Dr. Brooks mention cytopathic effects, and there's literature data on that. With regard to tumorigenic potential, again, as Dr. Khan mentioned, there doesn't seem to be any evidence at this point, unknown.

Can infection lead to human disease? And we've heard a couple of comments with regard to this particular issue for simian foamy virus. Insufficient data, certainly, and comments from presentations today are that the numbers certainly are low, and in terms of drawing conclusions from such low numbers is difficult.

Can the virus be transmitted from recipients? And, again, I think both the literature and in data summarized today indicate that yes for simian foamy virus within the non-human primate context, but insufficient data for humans. Certainly that's something, again, that given the low numbers, one has to be cautious in interpretation there.

Next slide.

Risk to the public, you know, in general. Exposure risk obviously is an issue in terms of persistence and transmissibility to other humans, multiple exposures, and an example I think was referred to in earlier presentations as well is the SIV. A number of instances where SIV has crossed into

humans, and again, with one of these resulting in pandemic HIV Group M.

Another issue addressed abrupt changes obviously in biological properties that may occur when passing through a new species that may result in altered pathogenicity or transmissibility.

Next slide.

Passage through an intermediate host may provide or remove selective pressures, resulting in genetic modifications in viral adaptation, recombination within the host with similar viruses can also alter the tropism, virulence, and drug resistance patterns, and although naturally occurs because of very low frequencies.

In a mean compromised host, exposure to the virus may generally allow for persistent infections, which allows for viral mutations to accumulate over time, and we've had a couple of questions to investigators about that particular issue, and again, I think more research clearly is needed in that area.

Next slide.

So in terms of sort of the broad risk considerations on this particular issue, at least from our way of thinking, clearly there could be no risk.

There may be insufficient evidence of risk, and there may be some evidence of risk, and that could range from both a low to a high level potentially, keeping in mind certainly within the regulatory context and perhaps broader than the regulatory context the need to act even in the absence of clear evidence is something I think that we all are -- certainly in the blood system is something that drives our thinking.

Next slide.

In terms of trying to distill some of the information certainly at least in our thinking in Health Canada, given some of the new data that we heard today and some of the data published in the Lancet earlier this year demonstrating transmission via transfusion, it seems reasonable for us that steps should be put in place to prevent transmission of simian foamy virus to the human population.

Next slide.

Now, what are the kinds of options that we could look at in terms of mitigating transfusion transmission risks in terms of broad spectrum options. One of them clearly is a public health measure, self-deferral. In other words, counseling individuals who have exposure risks either high or low to not donate blood.

Another option, donor screening and deferral, and this is one that we don't as regulars like to look at lightly. I guess the third bullet there, impact on blood supplies really are not listed in order of priority, but obviously that one is a very, very important one because we all understand how precarious supply issues for blood are, and clearly one has to balance a theoretical risk against the real risk of blood shortages. That clearly is a very important consideration.

There are still some other, I think, really difficult issues around an option for donor deferral, and that is that we don't really understand fully exposure risks in this particular area, and also even if we were to try and identify exposure risks, there is the issues around donor counseling and the more complex issues around any deferral action that we would consider that need to be further addressed.

Next slide.

Obviously donor blood testing is not an option at this point. The tests that Dr. Brooks and Dr. Sandstrom have developed in the labs, CDC, and Dr. Khan's are all research tests. There are no commercial tests at this point.

Another option is research and

surveillance, which really isn't an option because that's why we're here today, and that's something that's ongoing with regard to simian foamy virus.

Next slide.

When we're talking about potential deferral measures, again, what are the types of risk exposure that we could try and define at this point in terms of broad groupings? Obviously we've talked a little bit about occupational exposure to non-human primates. That's biomedical researchers, animal handlers, veterinarians or zoo keepers. These are individuals which at least from the perspective of time and types of exposures, scratching, biting opportunities, these would be the ones that potentially would fit into a high risk category.

Nonoccupational exposure to non-human primates, we've talked. James showed some data on monkeys as pets in terms of the numbers, very, very rough numbers. We don't have numbers in Canada certainly, and the study on the bush meat, Cameroon data. So that may or may not be occupational exposure.

Incidental exposure to non-human primates, and again, we're not clear whether or not or how often that occurs, individuals who may have been bitten or

scratched by a non-human primate. And perhaps there are other risk exposures that we're not aware of.

Next slide.

In terms of the way forward, at least our thinking within Health Canada is we have done some initial risk assessment that has been carried out by our Canadian Public Health Agency. We're refining that risk assessment to consider some of the data presented here today and some of the discussions from your committee.

We're having ongoing consultations with various stakeholders on this issue, including our blood operators, certainly if we move forward on any kind of blood deferral measures.

Next slide.

My last slide, just a series of acknowledgements to staff within Health Canada and our colleagues, Dr. Sandstrom and Brooks from Public Health Agency, for some of the thinking around this particular issue.

Thank you.

ACTING CHAIRMAN ALLEN: Thank you for that careful analysis. I think that was very helpful.

Where at this point do you see the Canadian Blood Services going in terms of addressing

this issue? That's probably what you were addressing in your coordinated risk management efforts, but have you begun to reach a decision?

DR. GANZ: Well, I think actually that's something for them. I know we have some representatives from both CBS and HemoQuebec in the audience, and perhaps they are better able to address their thinking on this particular situation.

But obviously we're looking at, as I've mentioned in the slides, we are looking at a series of options. One option doesn't necessarily exclude the other one so that we can certainly pursue options on the public health side in terms of providing advice to exposed individuals to self-defer and not donate. That certainly would be complimentary to more stringent regulatory measures to the blood operators.

ACTING CHAIRMAN ALLEN: Dr. Klein.

DR. KLEIN: I have a narrow question and a broader question. Let me ask the narrower one first. Does the fact that you have universal leukoregulation at all influence the steps you might take in terms of safety in Canada? And this is a cell associated virus like CMV or HTLV.

DR. GANZ: Yeah, that's a very good question, Dr. Klein. And actually I was going to put

it up on -- I used up my one slide on leukoreduction for the TSAC meeting.

Yeah, Canada has had universal pre-storage leukoreduction sine June of 1999. We implemented that particular process for a number of reasons, one of which was that it may afford some risk mitigation possibilities for any untoward agents transmitted through white cells.

So, yes, there might be some risk reduction already in the system, provided if the virus is white cell associated, but as you know, pre-storage leukoreduction isn't 100 percent effective. You're only reducing the titer of white cells marginally.

So, again, I'm not clear at all about infectious dose issues and so on with regard to this particular agent. Certainly in discussions with Dr. Sandstrom and with Dr. Brooks we'd like to pursue that particular issue through additional research, perhaps in the animal model system that James and Paul are using to look at whether or not, you know, components might afford different kinds of infectious dose.

DR. KLEIN: The broader sort of philosophical question is blood transfusion is a relatively small part of public health. If we all are so concerned about simian foamy viruses, isn't there

an issue about screening the animals and perhaps preventing importation of infected animals?

It seems like the animal handlers are at much greater risk than transfusion recipients at this point.

DR. GANZ: Yes, you're absolutely right on that one. Absolutely, I think we need to look at that, and that's why I actually mentioned it at the start, to say that, you know, we're focusing on a blood system here, but there are obviously broader issues.

I think certainly the issue that I raised, that was raised earlier in the CDC presentation and by others is the issue of affording a broader opportunity for a non-endemic virus to spread in the population.

ACTING CHAIRMAN ALLEN: Other questions. Yes, Dr. Lerker.

DR. LERKER: If I could just comment on the broader question, there is a program now underway at least in some of the major research facilities housing non-human primates to breed and maintain colonies of animals that are free of simian foamy virus, among a number of different other agents, other retrovirus, other herpes viruses. It's a very long, arduous process to get a usable size of a colony

going.

But if you tried to do that on imports, I think most of the animals, there would be no imports until things were implemented in the countries of origin. But probably where you were going with that. It is being discussed.

ACTING CHAIRMAN ALLEN: Okay. We'll move on to our last formal presentation: demographics of primate handlers. Dr. Nicholas Lerker.

DR. LERKER: Thank you very much. I'm pleased to be here today to talk with the Advisory Committee.

I'd like to try to do two things as the final speaker in this series. One is to try and address the issue of what kinds of numbers of individuals we're talking about when we talk about significant or exposure to non-human primates.

And then finally, I'd like to give the Advisory Committee perhaps a little insight into animal handling techniques over the years and how that can contribute to some of the human exposures that we're seeing the results of.

Next slide, please.

We know from doing individual jobs specific risk assessments in our own facility and

others, as well as some epidemiologic data that we published back in 1996, that there is differential exposure to both live and awake non-human primates as well as their body fluids, tissues, waste products, and so this is some of the demographic data that has importance in determining the significant risk categories.

Some of the job categories that we've tried to address individually are the veterinarian pathologists, animal, both husbandry and health technicians, biomedical researchers, behavioral observers, laboratory technicians, and then pet owners which don't necessarily fit into the occupational program, but I put them up here for analogy to some of the other categories.

In our epidemiologic studies, we found that obviously veterinarians and husbandry technicians were the most likely to handle live, non-human primates, and therefore, they're at the highest risk of the animal inflicted bite and scratch wounds.

In our epidemiologic study we found that the animal health techs were significantly more likely to be bitten than any other job categories. Veterinarians were significantly more likely to suffer body fluid exposure to mucous membrane. So there is

some differential risk associated with the different job categories.

I put the proximity to primates up here just for a point of discussion, and it was touched on by at least one of the earlier speakers, but this is significant just if you spend a lot of time around primates, you will know that -- I speak from experience -- that some species of primates are quite adept at spitting either saliva or mouthfuls of water at humans and also can throw feces with great accuracy over long distances.

(Laughter.)

DR. LERKER: And as I said, I can speak from experience with that, and these are primarily the apes. Chimps and orangutans are quite good at that.

So even somebody with sort of remote or distant approximation to non-human primates is not totally without risk. So I'd leave it there.

Just one other point I'd like to make is that in terms of the exposure opportunities for both the primate itself and its body fluids and feces and so on. The pet owner's profile resembles that of the two other high risk categories, the veterinarian and the animal health technicians.

Next slide, please.

Now, one of the problems is that in trying to determine the numbers of people that we're talking about in this discussion is these data are not readily available, and the approach that I have taken is to employ some enumeration methods, and what I've tried to do and I'll share with you is develop a sampling frame, and this is a specific initially for occupational exposures, a sampling frame that is organized by facility type.

And the rationale behind that is that facilities housing non-human primates that are a similar type probably have similar staffing ratios and so on. So at least for a first analysis, that's what we're trying to get a handle on.

Then we survey a subset of these facilities within each of the categories and try to get some idea of the numbers of workers in each job category, and then by applying those numbers from the subset to the larger sampling frame, we can get some data on the numbers that we're talking about.

This is the approach I've tried to use, and I should say at this point that this is very much a work in progress, and much of the data that I'll share with you today I got within literally a week ago at the meeting of the Association of Primate

Veterinarians, and so this is data that's still being developed.

Next slide, please.

So this is the sampling frame that I've developed, and this is the types of facilities that I've identified. This is the National Primate Research Centers funded by NIH, academic institutions, contract research organizations, various institutes and foundations, the big pharmaceutical companies and biotech.

Primate sanctuaries, this is a growing, increasing number of these facilities which provide sanctuary for primarily unwanted pets or former research animals, and it is a distinct entity from zoos, but there is a growing number of these facilities.

And then government and military research institutes. The vendors who provide monkeys for research and other purposes and importers, and then there are at least three commercial diagnostic laboratories that specialize in testing non-human primate samples, and so they are by definition exposed to the non-human primate body fluids.

And then among the zoos, 200 zoos, there are quite a few more than that in the U.S., but at

least 200 of them have at least one species of non-human primate on exhibit, and these are the estimated number of the types of facilities in the U.S. So they have identified so far at least 374 facilities in the U.S. that house non-human primates.

Next, please.

So this is a busy slide, but this is the same from the previous slide, and this is the number of subsets or the subset of different types of facilities that we have been able to survey over the last month or so.

And then in parentheses, it's just a percentage of the estimated total. So we have actually gotten data from 47 facilities representing at least one sample in each of the categories in the sampling frame.

And what this has allowed us to do is determine the mean number of workers in each of the job classifications of interest, in other words, veterinarians, pathologists, technicians in a broad sense, and biomedical researchers.

Next, please.

So to cut to the chase, what kinds of numbers are we talking about here? Using this approach, and again, this is preliminary data, we have

identified a potential of 14,500 individuals among all of the job categories who are exposed or have contact with non-human primates. If you look at the two high risk groups, the veterinarians and the technicians, the number is around 10,000.

Now, some of this may change. I didn't mention it, but on the previous slides where we have estimates of the average number in each of those categories, some of the confidence intervals are quite wide, and as we gain more data and sample more or survey more subsets, this data will change, but I don't really foresee any huge alteration at least orders of magnitude different.

So I think this is a reasonable ballpark figure for the total number of persons exposed to non-human primates in an occupational setting.

Next, please.

Now, I want to revisit the pet issue again because this is really the big variable in the equation in my mind. There's very little data in terms of the numbers of pets maintained or animals that are being maintained in private ownership, and I use the term "pets" to include other types of private ownership. There's quite a few non-human primates that are in the entertainment industry, and you have

probably all seen primates in movies and so on. So that's sort of what I'm talking about here in the broader term when I refer to "pets."

Many states have absolutely no regulations regarding the maintenance of non-human primates as pets, and even those that do have exemptions. California, for example, has one of the most stringent regulations regarding having non-human primates as pets, and new acquisitions have been banned since 1973 or around that time, but at that time they grandfathered in a lot of people who already owned these animals.

And so there are existing pockets of these animals, and their offspring are also exempt under the grandfather clause. So even in States like California, there are a fair number of animals, but an unknown number of animals maintained as pets.

There has been one single estimate that I've found, and this was referred to earlier, I think, in the opening remarks about the number of animals maintained in households in the U.S., and this is quoted to be or estimated to be about 15,000. This comes from a National Geographic article that they did on the non-human primate pets, and the quote is attributed to someone in the primate sanctuary

business, and some of this was based on the number of phone calls that sanctuaries were receiving by people looking for some place to take their pets off their hands because these animals are quite cute when they're young, but they are very unpredictable and become aggressive when they become sexually mature.

So the novelty wears off. These animals need someplace to go, and so the quote comes from that kind of assessment. Though it has not been verified or the accuracy, I haven't seen any real surveys about the accuracy of this number, but it's a working number for purposes of discussion.

The other question then is how many contacts are there in each household, and this is the highly variable issue. If you just assume there are 15,000 households and a minimum of two persons per household, then there's 30,000 individuals right there.

So the pet issue is quite the unknown in this whole equation.

And I just include this. We saw earlier Jane Goodal with the chimp, and this is something that I got off the Internet, and if you look on the Internet there's quite a bit of traffic in non-human primates in the pet trade or exotic animal trade.

And looking at that, this doesn't seem too unreasonable, but I just wanted to show that it's not just new world monkeys that are available and kept as pets. This is a baby baboon here, and this is a puppy, and similar to the quotation about pornography, if we're trying to define significant contact, it may be hard to define, but you know it when you see it. That is significant contact with an old world species.

Next, please.

This just shows the distribution of some of the major species in the facilities. Again, returning to the occupational side of things, chimp, baboon, African green monkey and macaque were the common old world, and virtually all of the facilities house macaques. Number of them also house chimpanzees.

And the human cases to date have all been where the species of origin has been identified, have all come from old world monkeys. No new work monkey infections have been identified as yet.

Next, please.

Now, I just want to shift. Well, just one other comment on the numbers impacting on the blood supply. At the break I got some information since I'm really not up to speed on what would be a significant

impact on the blood supply, and I'm told that there was an estimated 50,000 donations per day. The small number of humans here would be less than two days' worth of donations.

So at least from my own perspective or that at least puts things in perspective for me.

Finally, I want to talk about some of the trends and changes in animal handling that have occurred. One of the continuing areas to evolve are the use of personal protective equipment, and there is a large disconnect or some gaps in how things get done in different facilities.

For example, in the research end of things, full PPE is the standard operating procedure, and by this I mean gloves, long sleeves or Tyvek sleeves that are shown here, the dedicated uniform that is not worn off the premises, dedicated shoes or shoe covers, a face mask and eye protection, either goggles or a face shield. So this is sort of one end of the spectrum.

And the research facilities for the most part adhere to that end of the spectrum. The face shield issue was taken much more seriously in the mid '90s, actually the late '90s, 1998, I believe, following the tragic death of an animal handler at one

of the national primate centers from an ocular splash from a monkey shedding B virus, Herpes B or cercopithecine herpesvirus 1.

So I'll show the sort of evolution of where we are today in a moment, but the face shield issue and the whole issue of personal protective equipment in the research setting took on new meaning in the late '90s.

Zoos and sanctuaries appears somewhere in between on the spectrum. They may wear gloves and dedicated uniforms, but have not adopted the full personal protective equipment at least across the board.

Now, there is a new guidelines that have been issued or are out for review by the occupational health group of the American Association of Zoo Veterinarians, and so the zoos are moving more in this direction, at least in doing risk assessments and, for example, wearing eye protection when hosing is being done or handling of animals and so on.

At the other end of the spectrum, the animals in the private sector, very little, if anything, is being done in the way of personal protective equipment.

Next, please.

This just shows some of the evolution of the use of personal protective equipment over the years, and I was rereading some of the case reports and some of the original cases that reported bite wounds that occurred back the '70s and '80s, and you'll see why infection might be more likely to have occurred back then.

This shows some technicians that are restraining unaware, unanesthetized adult Rhesus macaque for tuberculin testing, no gloves, bare forearms, no eye protection, no mask. So bask in the '70s, that was the standard.

In the '80s we adopted the use of gloves for handling primates. In the '90s we added masks, and then in 2003, again, the eye protection although it doesn't help when the primate removes your eye protection for you.

(Laughter.)

DR. LERKER: But this is sort of the trend to more eye protection or more personal protection over the years to the current state.

Next please.

This just shows again some of the animal handling trends over the years. Again, back in the '70s, people hand feeding macaques without any

protective equipment whatsoever. Hand catching of primates was common in the '80s, into the middle and late '80s. The animals would be captured, removed from their cages using these heavy leather gauntlet gloves, and then the animal would be restrained and then the gloves would be discarded in favor of these vinyl or latex gloves.

And so you can see that learning this technique was not without risks, and so bites were very frequent and these gloves would not protect against a bite from an adult macaque with full canines regardless.

So we have moved away from that now, and we use a lot more of animals that are trained to jump into a transfer box. Again, the full protective equipment that's being used, and so the trend has been to more and more protection. So hopefully the risks associated with working with non-human primates now are not the same as they were in the '80s and '90s.

Next please.

Just in conclusion then, what can we say about the numbers or the estimates? Again, it's a work in progress, and I think it's valuable that we're -- it was eye opening to me about how difficult it is to get this kind of information and I think we'll

move forward and try and get a more complete view of the number of people exposed to primates both in occupational settings and as pets.

One of the things I wanted to mention and I forgot to mention when I talked about the calculations of the numbers. That only takes into account the staffing as it exists last week. It doesn't account for the turnover of people moving through these facilities, and there is quite a high job turnover in some of the positions at high risk, particularly animal technicians are from these entry level technicians, and people spend a short period of time and go elsewhere, and so there is a cycling of people potentially exposed and then moving on to other jobs that would not be captured in the kind of analysis that I showed you earlier.

And then finally just to hopefully -- current handling practices at least in the occupational setting should reduce the risk of the exposure, but not eliminate it completely.

So I think I'll stop there and answer any questions you might have.

ACTING CHAIRMAN ALLEN: Thank you very much, Dr. Lerker.

Questions? Dr. Lew.

DR. LEW: I don't know if you can answer this question, but I was just thinking about different cell lines. We use a lot of non-human primate cell lines in the laboratory, you know, for evolved cultures, all sorts of things, and I'm assuming that people are aware, but I don't know, you know, of the simian foamy virus problem. Is it possible that it's in different laboratories and that's another occupational exposure?

DR. LERKER: Yes, I think there are a number of cell lines that could harbor foamy virus. Most of our experiences that even in primary cell cultures where it's a problem, in fact, most of the attention before the recognition of the human cases, most of the attention to foamy virus was to get rid of it because it's a nuisance. It destroys continuous cell lines. You can go out maybe two passages and then the latent virus reactivates and you get a lytic infection that wipes out your cell line.

So there are cell lines, I think, that can harbor it. Also, some of the cell lines that apparently have that delayed, they don't have the predictable re-activation and lytic infection that they still are infected. I don't know what ATTC does to screen their primate cell lines for foamy virus,

but some of you might know that.

DR. LEW: The other follow-up question is has anyone looked to see if there was seroconversion of people that have worked for years with these different cell lines.

DR. LERKER: To my knowledge, they have not specifically looked at laboratory workers having worked with the cell lines for a long period of time.

There is one case that's associated with a laboratory exposure, but I believe that was primary monkey tissue and not a continuous cell line. So I don't think that has been done.

DR. KUEHNERT: Thanks for the presentation. It was very interesting. I just had a couple of questions.

One about, you know, you mentioned how PPE has changed over time, and I wondered if there were any data on actual needle stick and bite injury rates, whether that has actually changed over time along with the changes in practices.

DR. LERKER: We did a follow-up to our study that we did in 1996. We haven't published this, but we're gathering data. The bite rate has declined, which is good news at least in our facility. This is our facility.

The needle stick rate has remained about the same, and one of the interesting differences, for example, if you compare the needle stick rate of, say, a primate facility to a hospital, there's a different -- most of the needle sticks occur in the primate facility while the needle is in use rather than after use where it has been discarded, and this is because the primates move and jump and so on.

So that's one slight difference. I don't know if it makes any difference to exposure necessarily. But the needle stick rate has been fairly constant over the interval. So we need to think more about that as a risk factor.

DR. KUEHNERT: The other question I had was just about looking at the data, SFV and affected workers, that it looked like that people were first seropositive a while back, and so I wondered whether there are data on people who have only worked in the field since PPC was significantly changed and the techniques have been changed in the last ten or 15 years.

DR. LERKER: Well, I think that this could possibly be gleaned from the ongoing study that CDC is doing because they include a variety of people with a large -- what do I want to say? -- work history. I

mean some have worked for many years. Some are very new.

One thing also I didn't see in our earlier study, we did find that the incidence of accidents associated with non-human primate exposure in our study was much more or significantly elevated in people who had only been working less than two years.

And even with that frame, it's significantly higher in people who had worked six months or less, and so there's some kind of experience on training curve going on there.

But that's a good question. I think that will come out or could come out in the study that CDC is doing because they're getting histories on length of time exposed, I guess is what I'm saying.

DR. HENEINE: If I can add to what Nick just said regarding the duration of seropositivity, in our cases it is true that the majority have really longer durations, especially when samples are available for testing. But we did have a recent case where the duration was short, suggesting recent infection.

So we cannot fully exclude the possibility of recently acquired infections as well.

ACTING CHAIRMAN ALLEN: Other questions?

(No response.)

ACTING CHAIRMAN ALLEN: Okay. Well, thank you very much, Dr. Lerker.

The official timepiece says 1600, four o'clock. Why don't we take a break for 15 minutes? We'll come back and have the open public hearing. I've only got one person who is scheduled to speak, Dr. Kleinman again, and then we will move to the open committee discussion.

So we'll recess for 15 minutes.

(Whereupon, the foregoing matter went off the record at 3:54 p.m. and went back on the record at 4:17 p.m.)

ACTING CHAIRMAN ALLEN: We're ready to move into our open public hearing.

Is Dr. Kleinman in the room? Ah. Thank you.

Okay. Is there anybody other than Dr. Kleinman and his joint statement who would like to speak on this issue in the opening hearing.

Okay. Steve, I apologize. I need to read the statement to you for the third time today.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure

such transparency at the open public hearing session of the Advisory Committee Meeting FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement you advise the Committee of any financial relationships that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the companies or groups payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So if the Chimpanzee Owners Association of American have paid you anything, please let us know.

Good afternoon. Dr. Steve Kleinman, Chair of TTD. And it may amaze you, but on this issue I have no financial conflicts.

So I'd like to read the joint statement

from AABB, American Red Cross and America's Blood Centers.

SFV infections in humans has been recognized for a number of years. Newer studies have confirmed that humans working with primates in zoos or in research institutes in the U.S. may acquire this infection. It also appears that primate to human transmission has been occurring for many years in areas of Central Africa.

Because of the past experience with other simian retroviruses developing into human pathogens, and we have HIV-I, 2 and HTLV, AABB, America's Blood Centers and American Red Cross believed that continued concern over and study of SFV as a potentially transfusion transmitted pathogen is warranted.

Current knowledge indicates that SFV infects human peripheral blood leukocytes and establishes a persistent infection, and it can be detected for over 20 years. SFV does not appear to cause disease in humans, although the number of chronically infected persons undergoing follow-up is limited, I guess I would say very limited from what we've heard today.

Data about human-to-human transmission of SFV are sparse. Sexual transmission has not occurred

in six couples. And transfusion transmission did not occur in four recipients of blood components from a single SFV chronically infected donor.

There are many unknowns about potential transfusion transmission in humans if it occurs. As a high cell associated virus, it is possible that SFV will behave similarly to HTLV, such that one storage of red cells beyond 10 to 14 days would eliminate transmission. Two leukoreduction would greatly reduce if not eliminate the transmission risk from chronic carriers. And three, there would be no transmission from FFP cryoprecipitate or fractionated plasma derivatives. These possibilities could be tested in an animal transfusion transmission model, although there are some limitations in demonstrating lack of transmission as we've heard today.

There have been no studies of the prevalence of SFV in the U.S. blood donor population. Based on a limited number of research studies some broad risk factors can be defined including close physical contact with primates in the wild in Central Africa or in zoos and research institute outside of Central Africa. It is unclear if increased risk extends further to persons with more limited primate contact.

It should be noted that the current donor history questionnaire includes a question about previous residence in Central Africa, which appears to be a possible risk factor for SFV infection. Although it has been anticipated that this question may be discontinued as blood centers begin using laboratory tests capable of detecting HIV-1 group O.

In summary, limited current data suggests that SFV does not appear to be pathogenetic for humans. The prevalence of the agent in U.S. donors is unknown, but would be suspected to be very low. Transfusion transmission in humans has not been demonstrated, and if it were to occur the potential for detectable effect of leukoreduction and the risk from plasma products have not been assessed.

With the exception of definitively assessing the potential for SFV to be a human pathogen, we believe that the answers to all of these above questions could be obtained by performing well defined research studies.

Now, on a slightly different tack, in its investigations the CDC has adopted a policy of counseling SFV infected subjects to not donate blood tissue or other biological material. We agree with this approach. However, the deferral of a known SFV

infected person is a very different issue than adopting a deferral policy based on an attempt to establish an epidemiologic risk profile. Until further information is available, AABB, ABC and ARC believe that no additional questions should be added to the donor health history questionnaire. This document is already extremely long and complex and the addition of more questions with unknown benefit runs the risk of distracting donors from my more risk questions.

Furthermore, at this point it is unclear what criteria should be adopted to identify SFV risk and how a question could be worded to elicit such accurate information from donors.

Thank you.

ACTING CHAIRMAN ALLEN: Thank you, Dr. Kleinman.

Any questions for Dr. Kleinman on this statement? Okay.

Dr. Tabor, are you presenting the questions again formally or --

DR. TABOR: Could I ask for the last three slides in my presentation case?

The first question: In the absence of any known disease association should FDA be concerned

about the potential for transfusion transmission of SFV?

ACTING CHAIRMAN ALLEN: Comments, discussion on this?

Dr. Lew?

DR. LEW: I think it's a given we don't have enough data now to say if it's truly pathogenic. So, yes of course we should be concerned.

ACTING CHAIRMAN ALLEN: And I guess I would add to that that certainly in highly susceptible populations, i.e., for example people who are immunosurpressed, that is important. And we probably are using SFV simply as a place holder for other viruses that may be similarly transmitted, some of which we may know about and some of which we may documented in the literature that we were provided to read, and some of which we may not yet have identified. So, I would certainly agree with your summary statement.

Other? Dr. Cunningham on this?

DR. CUNNINGHAM-RUNDLES: Well, I guess the problem for all of us is going to be what does concern translate into to. So concern sure, but concern is kind of like not specific worry. So that's obviously got to have a second question: Okay, what do you do

about that? What can you do to solidify that concern into some fact.

ACTING CHAIRMAN ALLEN: Dr. Tabor, do you want to go ahead and run through all three of the questions.

DR. TABOR: Yes. We can go all through the questions.

Let me just add that I think that some of the thinking behind this question was at the last BPAC meeting it was felt there was not enough data to be concerned yet.

So let's go to the second question. Next slide, please. Do the recent evidence of SFV infections in humans and the evidence of transmissibility of SFV by blood and animal and animal studies heighten concern that known and unknown pathogenic viruses of nonhuman primates could enter the human blood supply?

And the next slide, please. Number three: Do the available scientific data warrant possible consideration of donor exclusion criteria for exposure to nonhuman primates? Please discuss the factors that should be considered.

Why don't we go back two slides, please.

ACTING CHAIRMAN ALLEN: Other discussion

on question one? Attempts to define the word "concern."

DR. DOPPELT: I just was going to say something similar. I think basically what your concern is a watchful eye. I mean, you're going to try and be observant, collect data. But right now you don't have much to hang your hat on, so --

DR. TABOR: Without focusing on the word "concern," the real question is does the Committee feel that the science suggests that actual transmission of SFV in the blood transfusion studies is an issue that we should be dealing with?

ACTING CHAIRMAN ALLEN: I'm going to go back to Dr. Kleinman's statement, the joint statement, and pick up -- this is on the second page, the second full paragraph the last full sentence. And he's listed some of the information that is known and some that is not known that should be known and then concludes: "With the exception of definitively assessing the potential for SFV to be a human pathogen we believe that the answers to all of these above questions could be obtained by performing well defined research studies." And I certainly would translate the word "concern" to be yes I think it needs attention. We need to continue with all of the

appropriate agencies of the Public Health Service, including certainly the FDA and its regulatory authority, the Centers for Disease Control, the NIH to be aware of this potential and continuing to monitor the situation very carefully and to fund and conduct research studies.

so, I mean, that's how I would translate "concern."

Yes, Dr. Klein

DR. KLEIN: I was just going to say that just the TT virus and GDBC and a number of other viruses were on the radar screen. This now, obviously, needs to be on the radar screen. And I quite agree that we need to not only continue to do the kinds of epidemiologic studies, but also the interventional research studies that are important until we can determine whether this is something that is a public health issue.

ACTING CHAIRMAN ALLEN: Dr. Goldsmith?

DR. GOLDSMITH: I guess I take a more cautious point of view than what I've heard here so far in a sense that this is a simian retrovirus and we already know about some of those as they're crossed the line from primates, from nonhuman primates to humans. They've caused different kinds of disease in

humans, and some have had long latency. We have heard about HTLV-1 today. And this could be a similar kind of an agent and that we haven't looked at long enough or in depth enough.

So I guess concern to me would be yes I am concerned. I would vote for being very concerned. And we'd like to have some additional information. And if by saying that we're concerned about this in the public forum, would that help people that CDC or elsewhere get more information from the public or get their job done quicker, then I think we should all be in favor of saying we're concerned and vote for that.

DR. TABOR: Could I just add? We've heard actually some good suggestions about areas for future research that come up in the discussion. I would just like to point out that this subject, this Simian Foamy virus ad blood transfusion and perhaps just Simian Foamy virus in general is most of the research is being done, most if not of all the research is being done in government laboratories. And this really is one of those things when people say what should we be doing research on in the government, we should be doing research on what no one else is going to do, that the private sector is not going to do. And this is probably one of those areas.

ACTING CHAIRMAN ALLEN: Are we ready to vote on question one?

Dr. Smallwood, would you --

DR. SMALLWOOD: All right. According to procedure, we must take a call vote.

Dr. Harvath?

DR. HARVATH: Yes.

DR. SMALLWOOD: Dr. Nelson?

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Cunningham-Rundles?

DR. CUNNINGHAM-RUNDLES: Yes.

DR. SMALLWOOD: Dr. Kuehnert?

DR. KUEHNERT: Yes.

DR. SMALLWOOD: Dr. Quirolo?

DR. QUIROLO: Yes.

DR. SMALLWOOD: Dr. Hollinger?

DR. HOLLINGER: Yes.

DR. SMALLWOOD: Dr. Goldsmith?

DR. GOLDSMITH: Yes.

DR. SMALLWOOD: Dr. Schreiber?

DR. SCHREIBER: Yes.

DR. SMALLWOOD: Dr. Lew?

DR. LEW: Yes.

DR. SMALLWOOD: Dr. Klein?

DR. KLEIN: Yes.

DR. SMALLWOOD: Dr. Doppelt?

DR. DOPPELT: Yes.

DR. SMALLWOOD: Dr. Davis?

DR. DAVIS: Yes.

DR. SMALLWOOD: Dr. Allen?

ACTING CHAIRMAN ALLEN: Yes.

DR. SMALLWOOD: And Dr. Strong, your opinion?

DR. STRONG: Yes.

DR. SMALLWOOD: Thank you.

The results of voting for question number one was a unanimous yes.

DR. TABOR: All right. We will proceed with discussion of the second question. Do the recent evidence of SFV infections in humans and the evidence of transmissibility of SFV by blood in animal studies heighten concern that known and unknown pathogenetic viruses of nonhuman primates could enter the human blood supply?

ACTING CHAIRMAN ALLEN: Dr. Hollinger?

DR. HOLLINGER: Yes, I think I understand the question. But we already know that. I mean, you got SIV and going to AHIV, you have STLV and HTLV. So when I read this initially I thought this is something we already know of the issue. And so I'm not sure on

how it helps the question.

Tell me what you're looking for in this?

DR. TABOR: Well, you know, I can't disagree with you when you say we already know about SIV and STLV. But when this report came out in March of 2004, it was accompanied by a commentary that raised the specter of cross species transmission beyond what we already expected. And so what we're asking you is -- what we're really asking you is should we be doing something based on a scientific understanding that this model could represent cross transmission that's occurring or could occur with other viruses? In other words, should we -- it really leads into the third question which has to do with types of donor exclusion. The question is do you feel that this model could represent a risk from cross species transmission from any of a variety of virus.

It looks like Dr. Epstein wants to add something.

DR. EPSTEIN: I think what we're really getting at is let's say we determined with some level of certainly or confidence that Simian Foamy virus is not a human pathogen, would we want to screen anyway because of a surrogate value for other things we might be concerned about known and unknown? So we're really

asking an opinion about sort of index of concern on the surrogacy question.

DR. NELSON: Well, by screen you mean incorporate this antibody screening donors? What do you mean?

DR. EPSTEIN: Well, we're not directly asking the Committee should we screen now for Simian Foamy. But we're saying would the issue of it being a marker for settings of risk for acquisition of simian pathogens be reason enough to develop a screening or testing program for Simian Foamy.

DR. TABOR: When you use the word "screen" though, Jay, I interrupt it a little bit more broadly. That could include a donor question.

DR. EPSTEIN: That is correct. In other words an intervention strategy. Is an intervention strategy for Simian Foamy, should we be considering intervention strategies for Simian Foamy because it may represent a marker for risk for other Simian zoonoses?

DR. HOLLINGER: Well, again, I think until you have a disease -- I think that of that commercial where is the beef. I mean, until there's a disease that one's established or that you have some association with a disease or an association with some

other retrovirus that's really substantial, I don't think you could do anything with that.

It says that we should probably continue some of the studies that have been outlined here today to look for these associations. That's very important. And one may or may not find any disease association whatsoever, but I think you have to look for it. And until that's the case, then I think this doesn't help us at all.

ACTING CHAIRMAN ALLEN: Let me disagree very slightly. And I agree that it seems like an obvious conclusion. Given the way that the government works, a positive response from the Committee on this is also a public statement from an expert committee in terms of adequate resources and allocation of resources. And that may be of assistance to the FDA if the committee believes that that's worth making such a statement.

Dr. Klein?

DR. KLEIN: I guess I'm slightly more concerned that this is an old world primate virus than I am that it's, for example, a porcine virus. But I am concerned about porcine viruses. I'm concerned about avian virus as well, and other animal species jumping the barrier. So in general, yes, I think I'm a bit

more concerned about this. But I agree with Blaine that I think we should put resource into looking at this virus. If you asked me how I would address the issue in general, I'd like to put a lot more resource into pathogen reduction technology for cellular blood components so that we could address all of these things rather than just this individual one.

So I think the answer is yes, I'm marginally more concerned at this point because it is an primate virus, but I'm still concerned about all of these others that we know can cross the species barrier and we know that some of them can cause human disease.

ACTING CHAIRMAN ALLEN: Well, but as I read this question it says "known and unknown pathogenic viruses of nonhuman primates that could enter." I mean, it does go beyond just the Simian Foamy virus.

DR. KLEIN: If they just to contrast the nonhuman primate, I am very concerned about those. But I am also concerned about other animal viruses. And so I think, you know, where do you start and where do you stop? Are you going to screen animal handlers out of the blood supply? How about pig farmers and chicken farmers? Again, I think the strategy

probably is not to in the direction from my opinion, but to look at pathogen reduction and put a lot of resource into this one that we're aware of now.

ACTING CHAIRMAN ALLEN: Dr. Strong?

DR. STRONG: I would agree with the yes answer to support research, which I think is the primary issue here. As Dr. Lew has mentioned, we don't have enough data to really say that this is a big problem.

I'd be a little concerned, though, by saying yes we're saying you should do something about the blood supply at this point in time. I think there's not enough data to support that answer.

DR. QUIROLO: I didn't really hear any data to support that this was a surrogate either. I mean, it seems to occur by itself. There's no other viruses associated with it that I -- unless I missed something.

DR. LEW: Well, I know there's no data that's been presented, but it's the unknown. If we did see Simian Foamy virus transmitted and you know that it came from a nonhuman primate source, so blood-to-blood there's always a possibility of that unknown. I think that's the only thing -- the way the question is read, that's what I'm assuming it's trying to

address. But I do agree that we all want more research, just not enough data to say let's change how we do things with the blood banks.

DR. QUIROLO: Yes. I'd hate to see screening for this because people were afraid it was a marker for something else, like we've done in the blood banking business in the past.

ACTING CHAIRMAN ALLEN:

DR. HOLLINGER: I did not read the question in that way.

Dr. Epstein, do you want to make any clarifying statements or --

DR. EPSTEIN: Well, I don't know if I'm adding clarity or confusion. But I think the idea of question one was is Simian Foamy a concern in its own right? In other words, what's the threshold of concern? And I heard that there's enough concern to keep it on your radar screen and do more research.

Question two is Simian Foamy further a concern because it might a surrogate for other things we might want to be worried about that could come from primates? And I'm hearing mixed opinions, and that's fine. But I do think they're different questions.

DR. TABOR: I wonder if I could also try to put it in a slightly different context, but I want

to be careful not to indicate any kind of regulatory approach. Because we haven't really discussed this beyond the preparations for BPAC.

First of all, there is an atmosphere in the blood community of wanting not to be behind the eight ball, but be out in front and be proactive with regard to emerging infectious diseases. And we've all heard discussions about whether things would have been different if we had had some measures in place, if we could seen the future before the AIDS virus entered the blood supply.

And the question here is are we -- and this was really, in a sense, raised by the Lancet commentary. Are we seeing a marker for what is going on and we haven't detected yet in seeing Simian Foamy virus cross species not really nonoccupational conditions, but more casual conditions than just between animal handlers and animals?

So if you were leaning toward adding a question or some kind of donor exclusion, the meaning of this question is would you do it solely on the basis of it as a model for other unknown viruses?

ACTING CHAIRMAN ALLEN: So you are asking whether populations at risk for infection by this virus represent the high risk behavior we ought to be

concerned in the context of virus behaviors?

DR. TABOR: I wouldn't word it quite that way, but I think we're really asking whether populations that are exposed to this virus are a high risk population for other retroviruses because of their contact. So in a way that's what you're saying, but with different words.

ACTING CHAIRMAN ALLEN: Dr. Kuehnert?

DR. KUEHNERT: I'm not sure if this is what you're partially getting at, but if we turn the clock back 30 years ago and had this same discussion and then became concerned and instituted a deferral for all these animal handlers and pet owners, it wouldn't have done a thing to stop the HIV epidemic.

So I'm not arguing against a deferral. I'm just saying that that's not going to stop a global pandemic. We need to be focused on transmission through blood rather than overall public health strategy. At least for this question.

DR. QUIROLO: Dr. Nelson?

DR. NELSON: Yes. I was just thinking about what Harvey said. I agree. I mean, there are a whole range of animal to human viruses, some of which are known to be quite pathogenic. And, you know, we could divide a fairly complex algorithm of screening

excluding all kinds of occupations. I mean, hepatitis E and, God knows. And it is worrisome that this is a primate, but nonetheless until I think we find either more evidence that it is a surrogate for a class of viruses that we could use it that way or in itself has even subtle pathogenicity over a long time.

One of the things that I think should be done is if there's pathogenicity, it may be quite slow and it would be interesting to find people who had been infected for quite a while, decades, and look what has it done to their hemologic system or what have you. And it might be possible to do that. I mean, that approach was taken a little bit with HTLV-1 and 2 short of the leukemia thing that eventually it was demonstrated that there was other potential for pathogenicity which made it important. Initially we didn't screen for HLV-2, but it was after some observation that we found that there was a reason. But there are a whole group of other viruses, even possibly some of the others that have recently been described. Under certain circumstances they're at least associated with pathogenicity, and the evidence is probably stronger than for these simian viruses.

DR. KLEIN: I must say I like the idea of getting rid of cell associated viruses because they're

getting rid of ones that we know are pathogenic, even though CMV isn't an enormous problem, it is a problem. Yes. And at the same time you're going to probably get rid of this particular virus, although that remains to be determined. So I guess as a surrogate measure I'm more in favor of getting rid of cell associated viruses than excluding people who may come in contact with primates now. I mean, next month it might change. You have new data.

ACTING CHAIRMAN ALLEN: Well, I guess it's that kind of thinking that lead me to read this question as being more of a research type question. But I've heard other discussion that suggested that maybe it's more of a regulatory type question. And I think that's a point I guess needs to be clarified before we actually vote.

The other point, you know we have had extraordinary evidence in the last three years in the United States of the potential for viruses to cause transfusion transmitted infection in a way that was never previously conceived. I don't think most people would have suspected the West Nile Virus, for example, could transmit and cause the disease that it did. And a tribute to our technology and to our surveillance systems now that we were able to pick that up so

quickly, do the investigations that were done and get a laboratory screening mechanism in place.

You know we are going to learn a lot more now because of the tools available to us compared with where we were 20 years ago.

Dr. Kleinman.

DR. KLEINMAN: Yes. My sense of this model issue, a sense of the discussion on this topic is actually the reverse of what we're talking about. And that is the reason that we're more concerned about SFV than we would be otherwise is because we've had the examples of SIV and STLV. I mean, if we just looked at SFV in itself and we didn't have these other retroviruses that had jumped and caused disease in humans, we would say there is no evidence of disease. And we're not linking it to other viruses that have disease, so therefore our level of concern wouldn't be anymore than it is for STLV or TTV, it's another virus. Lots of viruses are transmitted in the absence of pathogen inactivation. And we don't have technique to worry about all of them.

So I think we're actually being influenced by the fact that the reason we're not comfortable with the data on SFV is because we have precedents of other retroviruses causing human disease. And we're sort of

saying well maybe SFV, even though we don't think it causes disease, we can't really be sure. It might mutate and do the same thing.

So I don't see how SFV becomes the model for unknown pathogens. I see that SIV and STLV is the model for thinking about SFV as a potential pathogen in the future.

ACTING CHAIRMAN ALLEN: Other discussion on this second question?

Can I ask, just before we vote, can we have a quick show of hands among the Committee members who would like to see this interpreted more as a research oriented question versus a regulatory oriented question? Is that helpful at all?

Dr. Epstein?

DR. EPSTEIN: I think that confounds the issue for FDA. Because I think everyone would acknowledge the need to continue research on the possible pathogenicity of simian agents and also the possibility of co-infections and so forth. What we're really trying to establish here is where should we be going as regulators and is this concept of a marker agent itself a matter of concern. I just think the research issue is there, the regulatory question notwithstanding.

ACTING CHAIRMAN ALLEN: All right. Further discussion or questions or we ready to vote?

Dr. Smallwood, would you read the question?

DR. Klein, you look uncomfortable?

DR. KLEIN: I'm still a bit disturbed by this because I absolutely agree with Matt Kuehnert's statement that if we had used this as a marker -- if we had been smart in 1975 to say, you know, a monkey virus is going to jump the species barrier and cause a horrible disease so let's use this as a marker, we would have missed all these other things. It would have been the wrong marker. This is not a high risk group for HIV or HTLV; people in contact with old world and nonhuman primates. So from that standpoint I hate to answer this question yes because I don't think that's the right approach. On the other hand, I clearly am concerned about this agent because we don't know what its pathogenicity is and I think we need to keep an eye on it and other agents like that should they come into to our radar screen as this one has. And that's why I'm hesitate to say no, but I'm real hesitate to say yes because I don't know where that leads.

DR. KUEHNERT: I don't know. I think that

it's good that you listed all the questions, because the next question I think leads into that. And I wonder if we can answer question two a certain way and answer question three another way and still be consistent? And it may be because some of us are interpreting the question in a different way. But I feel like I could answer yes to this question and answer no to the next question and be consistent.

DR. HARVATH: I'm wondering if we could maybe maker a comment here about this past year FDA approach NHLBI for cofunding of a workshop in leukocyte reduction for looking at the reduction of various kinds of infectious agents.

And so what I would like to propose for question two is that personally I feel, yes, this is a concern. But what I would like to see is a more open scientific forum in which we take these things on, such as leukocyte reduction. What would be the feasibility of that actually helping us make inroads--it was in the context of, you know, TSE type agents, but let's take SFV as another agent.

I would say yes to question two this does concern me. But I would also like to say let's go forward with some scientific workshops to put more data on the table and look at some of the approaches

we could take in hand now, such as leukocyte reduction.

ACTING CHAIRMAN ALLEN: Dr. Strong?

DR. STRONG: Jay's comment about this being a question concerning surrogates, I don't see the word "surrogate" in this question. And I think that if this were in this question, that that might change our answer as well.

ACTING CHAIRMAN ALLEN: Dr. Cunningham-Rundles?

DR. CUNNINGHAM-RUNDLES: I was just saying yes we're concerned. And as Liana was just saying, sure we have concern but in what way does that change what we already said in number one? It doesn't add anything. We already said we're concerned. So number two shouldn't be are we more concerned.

So, I don't see what this is adding to number one currently, unless we add that word "surrogate," which most of us don't think is such a hot idea.

ACTING CHAIRMAN ALLEN: We do have options abstaining or what are the other options? I mean, yes, no or refrain?

DR. TABOR: Jim, I wouldn't agonize over it too much. I think our thinking was in question one

was SFV as a risk in itself. Question number two is SFV as a model, not necessarily a surrogate, but a model for what could happen with other viruses. We're certainly getting the benefit of the opinions that are being spoken around the table.

ACTING CHAIRMAN ALLEN: All right. Other questions or comments before we -- yes, Dr. Epstein?

DR. EPSTEIN: Well, just to point out there's the option of tabling the question and just taking any additional comments from the Committee members. Because the discussion is of value in its own right.

DR. STRONG: So moved.

DR. NELSON: I suppose one unknown risk that we've found with other retroviruses is recombination with somebody who is a carrier, let's say, of HTLV-2. And that does something that had the recombination not occurred, it wouldn't have happened. It's not a surrogate, but it's a biologic issue that could be a risk.

On the other hand, there are an awful lot more people who are infected with HTLV-2 than there are Simian Foamy viruses. And I suspect that that will probably continue. But whether or not that could produce a new strain that was more transmissible blood

transfusion or otherwise, I don't know.

So it's good not to have a virus with this characteristic, even though you're feeling pretty good at the moment with it.

ACTING CHAIRMAN ALLEN: Dr. Doppelt?

DR. DOPPELT: I would just emphasize a point that was just made a few minutes ago that if you voted yes on number one and you're a hair more concerned about number two, that still doesn't necessarily obligate you to vote yes on number three.

ACTING CHAIRMAN ALLEN: All right. Other comments before Dr. Smallwood?

DR. SCHREIBER: I would like to make a motion that we table this question. As Jay said, that's an option of the Committee.

ACTING CHAIRMAN ALLEN: Yes. I think the best way to do that, given the structure of the Committee, is just to express that, say table the -- abstain or table the question for the time being. Okay.

All right. If we're following *Robert's Rules of Orders*, I will accept that as an appropriate motion.

Dr. Lew?

DR. LEW: Does someone have to second it?

Because I'll second it if that's required.

ACTING CHAIRMAN ALLEN: Yes, it does need to be seconded. Okay.

The motion to table question two is open for discussion. Yes?

DR. DAVIS: Is this just to table question two, or will it also apply to question three?

ACTING CHAIRMAN ALLEN: No. This is just to table question two.

Dr. Lew?

DR. LEW: I think we're all sufficiently a little bit confused what FDA wanted us to address. And I think we've all said our piece, which I hope will be helpful to FDA.

ACTING CHAIRMAN ALLEN: I'm sure it will be looked at very carefully.

DR. QUIROLO: But I would agree with the question as it's written. But the comments that were made outside of the question made me wonder what the question really meant. But I agree that this virus is a great virus to study because it has crossed the barrier like these other simian viruses, and we've only looked at health people. So how many primate handlers have cancer and gotten chemotherapy and then what happened to that virus at that point? We've

never looked at that group of people or people that may be immune suppressed when they got a transfusion. So I think there's a long way to go here. But I don't think it should be used as a surrogate marker at this point.

Thank you.

ACTING CHAIRMAN ALLEN: Okay. Are we ready to vote on the motion to table?

I guess our Committee is such that you need to do a formal roll call, is that correct?

DR. SMALLWOOD: That is correct.

Your votes are being recorded in the --

ACTING CHAIRMAN ALLEN: We are voting whether or not to table question two. So a yes, it means yes I vote to table question two. No means I do not. Or you could abstain.

DR. SMALLWOOD: Just for the record, I'm just going to repeat what the Chairman said that the Committee is voting whether on the motion to table voting on question two. Okay. All right.

We're ready for the roll call.

Dr. Harvath?

DR. HARVATH: Yes.

DR. SMALLWOOD: Dr. Nelson?

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Cunningham-Rundles?

DR. CUNNINGHAM-RUNDLES: Yes.

DR. SMALLWOOD: Dr. Kuehnert?

DR. KUEHNERT: Yes.

DR. SMALLWOOD: Dr. Quirolo?

DR. QUIROLO: Yes.

DR. SMALLWOOD: Dr. Hollinger? Dr. Hollinger has left, and he was not privy to this motion.

Dr. Goldsmith?

DR. GOLDSMITH: Abstain.

DR. SMALLWOOD: Dr. Schreiber?

DR. SCHREIBER: Yes.

DR. SMALLWOOD: Dr. Lew?

DR. LEW: Yes.

DR. SMALLWOOD: Dr. Klein?

DR. KLEIN: Yes.

DR. SMALLWOOD: Dr. Doppelt?

DR. DOPPELT: No. I don't like loose ends.

DR. SMALLWOOD: Dr. Davis?

DR. DAVIS: Yes.

DR. SMALLWOOD: Dr. Allen?

ACTING CHAIRMAN ALLEN: No.

DR. SMALLWOOD: And Dr. Strong, our non-voting industry rep, your opinion?

DR. STRONG: Yes.

DR. SMALLWOOD: I thought this was going to be easy. Give me a minute here.

All right. The results of voting to table voting on question two, there were nine yes vote, two no votes, one abstention and the non-voting industry rep agreed with the yes vote.

The results of voting for question number one was a unanimous yes vote.

ACTING CHAIRMAN ALLEN: The motion to table carries.

So a tabled motion can be brought back at any point. This was not a motion that gave a specified time to bring it back. So, Dr. Epstein, we would consider it at some future point if the FDA wishes to bring it back up.

Let's move on to question three.

DR. TABOR: The next slide, please.

Do the available scientific data warrant possible consideration of donor exclusion criteria for exposure to nonhuman primates? Please discuss the factors that should be considered.

ACTING CHAIRMAN ALLEN: This question is open for discussion.

DR. KUEHNERT: Could I just ask a point of

clarification first? Is FDA looking for a discussion or looking for a yes/no vote here?

DR. TABOR: I believe both.

ACTING CHAIRMAN ALLEN: Unless the answer were clearly, you know, an unequivocal no, but I think in that instance they would still be very interested in the discussion and considerations. I think that the discussion is going to be important regardless of which way the vote actually goes.

DR. KUEHNERT: Okay.

ACTING CHAIRMAN ALLEN: Dr. Klein?

DR. KLEIN: Well, I think you have to start by saying that any kind of exclusion would have a minimal impact on the blood supply. I don't really think that that's a major issue. So you might say then what's the downside of doing this? And I think there are two major issues that I feel are a downside.

The one is that I can't think of all the questions that could be put on the donor screening form. In fact, I can think of a number of questions, and it's frightening. And I think that if we have enough of those already that may not really protect the recipient of blood transfusion. So I think that's one reason.

The other reason I think it does set a bad

precedent. I think it sets the precedent that you could say it's the Crever principle, but I would look at it the other way around: We really have no evidence at all that this a public health threat. So I think it's premature to do so.

That's my discussion. And you'll get my vote later.

ACTING CHAIRMAN ALLEN: Dr. Quirolo?

DR. QUIROLO: I think the wording of exposure would lead to a lot of self-deferral as people wouldn't really know what that meant. So if my neighbor has a monkey, did that mean that I have been exposed to that monkey and I can't donate blood?

ACTING CHAIRMAN ALLEN: Depends on what the monkey threw at you.

DR. QUIROLO: Yes, well or spit at me.

So I think that the way it's worded, besides what Dr. Klein had to say, it's very ambiguous.

DR. TABOR: What we were hoping to get here was your opinion on exclusion criterion in the very broadest sense without trying to narrow it down to any one set of criteria. Just whether we should be considering exclusion criteria. And then if you gave us a yes vote, the second half of it would be for you