defined distinctions. So at present, even though you can frame it just as you indicated, and we probably would, practically that's why I asked the question earlier.

You know, how long will we need to wait until people are convinced that this is not a problem and we can reverse this policy? And what I heard was, you know, it's probably five or ten years before we'd have a sense.

So, you know, do you want to tell people, you know, call back in a year or two? So I think practically this will be -- you know, unless there is some position of this committee that this should be a two year, you know, revisited, I think it would be inappropriate for the blood banks to communicate to the donors that this is a temporary deferral.

CHAIRMAN BROWN: Yeah, I understand that point of view. At least this is not complicated by the necessity of retesting. I mean, that's at least one thing we don't have to worry about.

DR. BUSCH: It could be viewed as a good or a bad issue. I mean, --

CHAIRMAN BROWN: Both, both. From the point of view of basic science, bad. From the point of view of practicality, good.

The final scheduled -- I'm sorry, is there a question?

Bob.

DR. SCHONBERGER: Mike, I'd like to come back to this question of deferring for history of prior use of blood products, which, as you know, is one of -- I feel is one of the best things you could put in place for building a fire wall between us and the expansion of any inapparent infection that might be occurring through blood and blood products via TSE agents.

And this number that you come up with of seven or eight percent, what I'm having difficulty with this is making that -- it seems to conflict with the experience of Marian Sullivan and trying to do look back studies where it seems like a much larger percentage than that of people who have received transfusions at least have died already by five years or so in the look back.

And presumably, if the people who survived transfusion are such a small cohort, a lot of them aren't going to be healthy enough to give blood anyway. And is that really a realistic number, or could it be smaller than that?

DR. BUSCH: I think that number is

definitely accurate. You know, it's coming from -- we're required to ask donors have you been transfused in the past. So this is a required question of blood donors, and these are compiled, actual reports from blood donors.

I think the issue is -- you're right, you know, half of blood goes into patients who die, but actually only a small fraction of transfused patients die, probably 20 percent. And the distinction is, is that the patients who are dying get a heck of a lot of the blood.

So very ill patients consume a lot of blood. Eighty-percent or so of people who are transfused survive, and those people probably -- many of them, fortunately, currently become dedicated donors because they've benefitted from the transfusion process.

But the number of 78 percent I'm certain is correct.

DR. SCHONBERGER: Well, what if you excluded albumin?

DR. BUSCH: That's not included in that.

DR. SCHONBERGER: That's not included?

DR. BUSCH: No.

DR. SCHONBERGER: Okay.

CHAIRMAN BROWN: Questions from the floor?

DR. TABOR: Well, the question about history of transfusion is the one that predates the availability of most of the serologic tests we have, and it's clearly one that, sometime in the future, could be reexamined.

It's certainly been well documented that most people, for instance, of those very rare cases of individuals whose blood transmit hepatitis B, they've almost never had a history of transfusions themselves. So that question is -- that we ask donors is an anachronism and probably is an anachronism with regard to new agents also.

I'd like to also make a comment regarding the use of the term British donors. We're not talking about British donors. We're talking about red blooded, American donors who happened to have had enough money to go to England or to have been sent there by the military.

Where possible, I think we should not refer to them as British donors because that adds a level of connotation that we're excluding something alien. And we're talking about American blood donors who are going to be impacted by what we decide, and it's the American blood supply is going to impacted.

CHAIRMAN BROWN: For the record, that was Dr. Tabor from FDA.

So the transcript is hereby directed to strike out every use of the phrase British donor, which is, in fact, incorrect; and these obviously are American donors who have visited or lived in Britain.

Although I suppose British donors would still be included, wouldn't they?

(Laughter.)

CHAIRMAN BROWN: We haven't addressed that.

Larry.

DR. SCHONBERGER: I'd like to suggest to the Captain -- I guess it was Captain Gregory that presented to us where -- Rutherford, was it?

CHAIRMAN BROWN: Captain Rutherford.

DR. SCHONBERGER: Rutherford.

CHAIRMAN BROWN: Close.

DR. SCHONBERGER: Okay, sorry about that. Bruce Rutherford.

That when he talks of 55 years of data, you know, where there's been no cases and so on, that it would be more impressive if the military could institute or present sort of a more epidemiologically oriented study.

I would think that they are particularly uniquely suited to potentially get good data on the new variant CJD issues particularly, and they still would have time to set something like that up, since much of the exposure of the U.S. citizens to Europe, I would think, may well be military people who were assigned there during the '80s and so on.

Perhaps the military could identify these people. And certainly the Centers for Disease Control would be happy to help continue the follow up of such individuals if they would want to institute that.

It just struck me when we're talking about all these years of not hearing about things, when, in fact, we search often to look for tighter epidemiologic type of studies, and I would encourage that that be discussed.

CHAIRMAN BROWN: Yeah, I don't know we need to discuss it now.

But Captain Rutherford, you've got an offer for help if you -- from the CDC if you'd like to -- and I think Larry's right. You have an unusual opportunity, in fact, to assess this problem in the near future and CDC is a good colleague to have.

The final scheduled presentation is Dr. Richard Davey, who is the Chief Medical Officer for

the American Red Cross.

DR. DAVEY: Thanks, Dr. Brown. Just before I start, I'd like to correct perhaps one misperception from Mike's presentation. He said that half of patients who get transfused eventually die.

Actually, all patients who get transfused will eventually die.

(Laughter.)

DR. DAVEY: So, Mr. Chairman, the American Red Cross does welcome the opportunity to speak to this committee on this important subject. The Red Cross supplies almost half of the nation's blood supply through the generosity of over four and a half million volunteer blood donors.

We serve over 3,000 hospitals through our national network of 37 blood regions. The Red Cross regards the safety of the blood supply as its highest priority. As such, the Red Cross is currently conducting nucleic acid testing for HCV and HIV throughout our system under an IND application.

In addition, Red Cross scientists are actively investigating possible emerging threats to the blood supply such as Chagas disease and Babesiosis. We've also supported research in the TSEs through direct research conducted by Dr. William

Drohen at our Jerome Holland Laboratory, as well as through -- as well as with collaborative research with both Dr. Brown and with Dr. Rohwer.

The Red Cross actually has devoted more resources than any other private organization to understanding the relationship, if any, between TSEs and blood transfusion. While the safety of the blood supply is our highest priority, the Red Cross also has an additional responsibility to ensure an adequate supply of blood and blood products for the American people.

Indeed, an inadequate supply of blood poses a major safety hazard, as critical blood and blood components may not be available when needed. We view with considerable concern, therefore, any proposal to defer donors who have lived in or traveled to Great Britain during the peak years of the BSE epidemic in that country.

This deferral is being considered because of the theoretical risk of transmitting new variant CJD from individuals who may have consumed beef products in Great Britain during those years. As we know, new variant CJD has not been reported in the United States, and there are no documented cases of this disease being transmitted by blood or blood

products worldwide.

Now this morning Dr. Alan Williams presented data gathered through the REDS and ARCNET systems on the impact on the American blood supply if donors who lived in or traveled to Great Britain between 1980 and 1996 were deferred.

In brief, the percentage of donor travel to the UK varied from 0.4 percent for those who resided in the UK for five years or more to 22.6 percent who were in that country for three days or fewer.

The estimated annual blood resource lost by deferral of donors visiting UK between 1984 and 1990 varies from over 35,000 units lost annually for deferral for a five year visit to 1,939,000 units lost for deferral for a one week visit.

That's just an annual loss, not a cumulative loss, which would be larger if we looked at it over a two or three or four year span.

Now the blood supply today is marginal, at best, with shortages often occurring over the holidays and summer months. A variety of recruitment strategies have been implemented with encouraging results, but the donor base remains barely adequate to meet increasing clinical needs.

Our blood supply actually is not very elastic. Increased recruitment efforts, however strenuous, may not be able to overcome the deficit caused by deferrals of the magnitude being considered by this committee.

New donors would have to be found to replace the deferred donors. As these new donors, as we've heard, would be first time donors, most of which would be first time donors, a group with a higher incidence of deferral risk and disease markers, it's quite possible that these new variant CJD deferrals would actually decrease the safety of the blood supply.

In addition, deferred donors may face possible stigmatization for being somehow unsafe, and may have undue concerns about being at risk for a dread disease. Also, and I think this is important, the message that the committee will send to the public with these deferrals is that Mad Cow Disease is a current blood transfusion safety risk in the United States.

Can we say the new variant CJD will never be shown to be transmitted by blood transfusion? Of course we can't. That would be asking us to prove a negative when we can't do that. But we must act

rationally using the best science and professional judgement in considering these options.

Research must continue in this important ~~a~~rea. Periodic evaluation of our national strategies on blood safety issues must take place. However, given the present body of scientific and epidemiological data, and considering the known impact on our nation's blood supply, any deferral at this time for this theoretical risk cannot be justified.

Now I may just digress from my written comments for a moment. I think this committee clearly has a very important issue in blood safety and it's considering it very, very carefully, to its credit. But I think it's important for us to realize that not having enough blood is a very, very unsafe thing.

In the National Blood Data Resource Center data that wasn't presented today, 8 percent of the hospitals in the United States in 1997 -- 8 percent -- had to defer or cancel surgery because there was not enough blood.

That's a lot. That's within the Red Cross system and across the nation in the independent blood centers, 8 percent of hospitals deferred surgery.

We just don't have enough elasticity to make up for a further major deferral. In the Red

Cross system, we are actually increasing donations. Our donations are up, but the demand is up even further.

We also have to consider again the first time donor issue. We're going to be replacing these deferrals, if we can replace them at all, with first time donors primarily.

And we've seen that they have an increased risk of deferral risk factors three times over repeat donors, increased risk of disease markers of twice that of repeat blood donors, a safety issue of concern.

Also, I think we have to ask is it in the public interest, as Mike pointed out just a few minutes ago, to have to convey a message to our donors, most of whom are dedicated pheresis donors and repeat donors, that we no longer wish to have them as participants in the national blood supply.

We will develop a group of hurt, angry and scared donors. And whether deferral is permanent or temporary, it's going to be very hard to give these folks the message that they're deferred for a risk that really we know nothing about and is purely theoretical.

It's up to the blood centers to have to

deal with these donors. It's up to the blood centers to have to get new donors, and that's going to be tough indeed. And again, I think it's important to realize that public perception of the safety of the blood supply is also at question here, and deferrals will indeed raise the public perception of risk of TSE in the American blood supply.

So I ask the committee to think very carefully about these proposals and to base their decisions on the best science and epidemiology available. Consider the impact of blood safety that may result from significant erosion of both our blood donor base and of public confidence in the safety of the blood supply.

The American Red Cross will continue to conduct and support research on the possible transmissibility of new variant CJD, and we will honor our commitment to help ensure both a safe and an adequate blood supply for the American people.

Thank you.

CHAIRMAN BROWN: Thank you, Jay.

If there is anyone in the room who wishes to make a statement, this is the time to do it.

Oh, I'm sorry, did you -- Peter, a question for the last speaker or a comment?

DR. LURIE: To the assertion that the development of travel restrictions would signal to the public that Mad Cow Disease is a problem, I guess I have two comments. The first is the Institution of Travel Restrictions for Malaria does not seem to have communicated to the American public that malaria is a problem in the blood supply.

What I think the message the American people will take from this is that a group of people have wrestled with the problem and have done the most they can to protect the blood supply from Mad Cow.

CHAIRMAN BROWN: I must say the Chair agrees with Dr. Lurie on this. I don't think it probably is too smart to go that far afield and make a decision on the basis of something which really is a question of education.

I mean, if someone is going to take a decision to defer, let's say, a small number, let's just say, of donors who have lived in Britain as evidence that Mad Cow Disease exists in the United States, I just don't think there's much we can do about it.

That's just a question of not understanding. In any case, we had a question or a comment from the floor.

DR. FREAS: Please identify yourself.

MS. McMILLAN: Certainly.

My name is Melissa McMillan and I'm with America's Blood Centers. And I just wanted to comment a little bit about some of the things that Dr. Davey mentioned. America's Blood Centers is the association of all the independent community blood centers.

And also, like the American Red Cross, we do collect about half of the nation's blood supply. We work with about 3,100 different hospitals and serve about 125 million people annually. I think some of the things that we've heard today -- we've heard a lot of scientific data.

A lot of the things I'm about to tell you are based upon conversations with the communication structures and our members who are located in 46 states, and also based upon some of the shortage surveys that we conduct to try and monitor the status of the blood supply during our tradition shortage periods which are, like we've discussed, the summertime and the wintertime.

We have had several members tell us that, even as of last summer, their transfusion rates increased not just the 3.7 percent we heard today, but 15 percent. Another center in Florida said that their

transfusion rates increased last summer by 20 percent.

Now, if you take it nationwide, you do have a much lower average; but these people are -- and the donor recruiters are spending an increased amount of time and money to bring in donors when their transfusion rates are soaring far beyond the expectations of the recruitment goals that they set based on a typical need.

Now, this is something we need to look at. There are a lot of things that we need to, you know, think about. And some of this data we don't have. For instance, what are these transfusions being used for, what types of surgeries?

This data is not readily available, but it could give us an incidence as to what are the types of people that need surgeries and maybe also give us some sort of correlation among the people who are donating.

For instance, we have liver transplants on the rise. With an aging population, we're going to have an increase in the number of knee and hip replacements. These surgeries require a lot of blood.

Now, I've had many reporters over the years ask me, "Has anybody ever died from a lack of blood?" The answer is no. But do we want to take a chance in saying that? We have to possibly say yes if

we defer a percentage of the population who are good donors.

I just think it's something we need to think about.

Thank you.

CHAIRMAN BROWN: Is there anyone else in the room who would like to make a comment?

Yes, middle of the room, left-hand side.

MS. SULLIVAN: Thank you.

I'm Marian Sullivan from the National Blood Data Resource Center. I was sitting back there trying to decide which of my data to defend first here today, and I decided to speak for a couple of minutes about our year 2000 projection.

The projection, which has been quickly flashed on the screen a couple of times here today, could benefit from being put in better perspective, I think. Without the benefit of the other slides that led up to its presentation at the advisory committee meeting, it's a little bit difficult.

The projection resulted from an 18 month data collection and analysis process which involved 2,400 U.S. hospitals and blood center participants. As a result of this 1998 nationwide blood collection and utilization survey, the NBDRC and Westat produced

national estimates for blood collections and transfusions in 1997.

These data were compared primarily with data from the Center for Blood Research -- which had been collected by the Center for Blood Research for 1994, the last year for which national data were collected prior to our survey.

However, we have also conducted an analysis of historical trends going back well into the 1980s. Considerable fluctuations are evident over these years. The year 2000 projection graph which you say today illustrates the trends in supply and demand for the most recent and most relevant period based on the 1994 and 1997 data.

The supply declined by 4 percent, or 1.3 percent per year, in this period. If I had my slides with me today, you could see that if we plot whole blood collections back to 1989 through 1997, the overall decline is 11 percent, or 1.4 percent per year, from 14.2 million to the 1997 figure, 12.6 million.

In fact, the slide which you did see today actually extrapolates the available supply rather than total whole blood collections. And this has somewhat softened the negative slope which you might have seen.

And that's due to the fact that we have seen, during this period, a significant decrease in the test loss percentage which has softened the slope if we plot available supply, and that has been taken into account in our projection.

Regarding transfusion demand, the extrapolation which you saw illustrates a 3.7 percent increase in transfusion -- units transfused between 1994 and 1997, or 1.2 percent per year, which is not statistically significant.

In fact, if I had chosen to plot allogeneic, meaning community units transfused, you would see an increase in transfusions of 7.1 percent, which is significant. But the projection actually included all types of donated units transfused.

In fact, if you can once again imagine my absent slide showing historical trends back to the early '80s, what you see is that annual transfused units have actually leveled off since the early '90s. And prior to that, there was a very steep increase in the early '80s followed by a decline that began about 1986.

We do not believe that we have overstated this issue in our year 2000 projection. The assumptions we made were based on the most recent

trends in collections and transfusions.

In fact, after I presented these data at the advisory committee meeting last month, a number of committee members, some of the speakers and some others closely involved in blood banking commented and seemed to agree that I had actually understated the problem.

And if, in fact, we had included other factors and prepared a more complex model, other factors such as the population increase and the redistribution of the population, as well as blood group availability -- if we had factored these things into our model, then the projection would have only been strengthened.

Thank you.

CHAIRMAN BROWN: Thank you very much, Marian, for a well tempered riposte to the criticisms.

I think -- Ray, is it about this? Because I was going to suggest that all of the people who have made public presentations stand ready to answer questions when this aspect reappears, which it will, almost immediately, if that's okay.

Marian, you'll probably be recalled to the stand, okay?

That concludes the public hearing part of

our day and we now enter into deliberations, which is always the most amusing part of each day.

(Laughter.)

CHAIRMAN BROWN: And I have a plan. And it will probably get sunk, but I want, before we make these deliberations, to summarize for you and the committee members my own view of the framework for the following discussion.

We have, on the one hand, to evaluate the risk of disease transmission from the blood of patients with new variant CJD. That is the issue before the committee. And here is what we know and don't know about that side of the equation:

We cannot yet predict the magnitude of new variant CJD in the United Kingdom. We cannot quantify the risk of infectivity versus the period of potential exposure. We do not know the proportion of new variant CJD cases that will have infectivity in the blood, if any.

We do not know the level of infectivity, if any, in the blood during the incubation period of new variant CJD. We do know that there is probably a much less degree of risk in plasma derivatives than in blood components based, as a generality, on what we know experimentally from what you've heard a little

bit of this morning and a good deal of in December, this being based on both the distribution of infectivity in TSEs, transmissible spongiform encephalopathies, in general within blood components.

That is to say, largely present, but not exclusively present, in the Buffy coat. Plus the fact that processing of plasma for derivatives has been unequivocally shown to result in very large losses of any infectivity that might have been present in unprocessed plasma.

The second part of the equation is the effect of any exclusion on blood supply. And we've learned that we have a good quantification of the effect on voluntary donor supply. We have no information at all on the effect on paid donor supply.

And that's what I come away from this morning's education as the main elements of our consideration. It therefore appears to me that if any exclusion is, in fact, recommended, it is going to have to be done as a pragmatic decision.

In other words, can any cut be made to obtain a maximum reduction in risk with a minimum effect on the blood supply? I propose to ask the committee -- and Bill, if you want to put that slide on now -- to immediately consider a reversal of the

draft questions in which we will consider question 2(a) first.

And what I'd like to do -- as you see, this is a query about doing any exclusion for the purpose of plasma derivatives. And it's possible that we can dispense with this question immediately. It's possible we may not be able to.

I therefore wonder if the committee would agree to answering that question even before discussion with a yes or a no. If the majority of the committee feels that there is no need to recommend new criteria for deferral with respect to plasma derivatives, we can dispense with question two all together and concentrate on question one, which is the same question focused on whole blood donors.

If the committee decides that question two needs discussion before any decision is made, we will go ahead and duly discuss it. This, by way of perhaps spending more time on what appears to me, at least, to be a question of -- that is arguable on both sides, that is question one.

If the committee would like not to do this, please let me know. If you'd rather just sort of take it 1(a), 1(b), 2(a), 2(b) as it's written, then we'll go ahead and do that.

Stan.

DR. PRUSINER: I would like to argue that we go as planned in the beginning, 1(a), 1(b), 2(a), 2(b), because I think that there's some -- there can be some arguments made with the first group of assumptions that you made, pieces of data that you threw out about prions being largely in white cells, blood product titers being lower.

So I would suggest that we don't change the order, --

CHAIRMAN BROWN: Okay.

DR. PRUSINER: -- that we don't do this.

CHAIRMAN BROWN: Bob.

DR. ROHWER: I also think we need to consider, in general, the intent of dividing this into two categories and what the significance of that is. In other words, I'd remind you that the British right now are not deferring for fresh blood. They're only deferring for plasma.

It's just the opposite of what the intent, I believe, of this -- of the focus here is. And there are important implications of that, and I could begin by discussing those right now or we can resolve this issue of whether we're going to discuss them first.

CHAIRMAN BROWN: Well, is the committee

more or less agreed that it would be a better idea to just go through 1(a)(b), 2(a)(b)? I hear lots of heads shaking.

Okay, the Chair stands demolished.

(Laughter.)

CHAIRMAN BROWN: And we will therefore open the discussion with a discussion of question 1(a): Should the FDA recommend new deferral criteria for whole blood donors to attempt to reduce the theoretical risk of transmitting new variant CJD from transfusions based on foodborne exposure to BSE in the UK?

The question is open for discussion.

Yes, sir.

DR. CLIVER: I'm going to get this in sooner or later anyway, so now's as good a time as any. I've been hearing wish lists of things that need to be researched. We also heard don't wait for the science, but eventually all of these things are going to be resolved, we hope, by scientific investigation.

We're dealing with a pyramidal hypothesis here that is all based on a broad assumption about food transmission. And as I said at the previous session, I'm really dissatisfied with the way this aspect of the question was being addressed.

I think we need to know more about that, if we can. But just the idea that now we're going to focus on transmission from person to person via blood and give up, as it seems to me, on some fundamental aspects of how people got infected via food in the first place I think is not the way to go.

So just to give you an idea of the things that I think we ought to be trying to know more about with regard to peroral transmission in beef, if you will, or animal products -- one, I understand that there is some work that addresses the question of the level of agent in tissues -- specific tissues eaten.

I'm hoping that that also addresses the question of -- the degree to which this is a function of the stage of the infection. We're hearing that perhaps the last year or so before onset is the time when the agent is going to be at peak, and I'd like to know whether that's universally true or whether it's even applicable to the perceived edible portions of a carcass.

Second, we don't know anything about the digestibility of the various tissues that may harbor the agent and how those are going to be processed during the digestion in the GI tract.

Third, assuming that the agent gets to a

susceptible portion of the intestinal mucosa, and we don't know what that is, why then the question is what is the interaction between the agent and the intestinal mucosa?

That's just one cell defending us from all the things that go through our bodies all our lives and this is a pretty critical aspect.

Finally, it seems to me that we ought to be addressing the question of age and other host factors. That is, as people, how differently do we process these things?

When I hear that onset of something that might be CJD in someone under 55 is probably diagnostic or at least highly suggestive of new variant over 55, it isn't seriously considered, this says that something happened to me a while ago and, if I want to go back to England and eat beef, I've got a carte blanche now because I'm 64 and it ain't going to happen to me.

So, you know, I should be able to donate blood forever, except, unfortunately, I had something 12 years ago with a melanoma that kind of negates that. But we need models. We need to be trying to find experimental means of addressing these and I'm sure additional questions.

And they aren't going to solve any problems real fast. But all the same, to proceed with the top of the hypothetical pyramid and ignore the base, I think, is dead wrong, too.

End of sermon.

CHAIRMAN BROWN: Yes, Bob, I'll call you in just a second.

Dr. Cliver, it's possible that there's a misunderstanding here. We are not here to discuss how people get new variant CJD in Great Britain. We're not concerned about how they got it. We're just concerned that they got it.

And what our main concern is, what our only concern is, is whether or not such patients are capable of transmitting CJD through the blood.

DR. CLIVER: But risk assessment is a well established part of the way these kinds of decisions are made in the regulatory arena, and we don't have the bases for risk assessment vis-à-vis how long somebody stayed in the UK, what they had to eat, how they at it and so on.

So I think it's a valid and significant part of the risk assessment process.

CHAIRMAN BROWN: Yes, you're suggesting that we really ought first to decide -- have a

consensus on how new variant -- whether or not living in the United Kingdom is a risk factor?

DR. CLIVER: I didn't say that. We're talking about quantitative risk assessment, and I didn't say that the data are in hand to be able to do it.

All I said is while we're prescribing or wishing for research that would clarify some other aspects of this hypothetical pyramid, that neglecting the base of the pyramid by saying that's not relevant, we've got to get on with business, is incorrect.

It is just not the way risk assessments are done -- quantitative risk assessments.

CHAIRMAN BROWN: What way are you suggesting that we do here now?

DR. CLIVER: I'm suggesting that we at least add this to our wish list of things that need to go into a longer term perception and understanding of whether someone in this country who happened to spend a few days a few times in England, as I did, is at risk as a blood donor and is endangering his fellow citizens by giving blood.

CHAIRMAN BROWN: Right. So, again, I don't think we disagree. Everybody would like to have that, and we probably will have it too late.

DR. CLIVER: Well, okay. But all I'm saying is it isn't -- I haven't heard it even mentioned on the wish list at this point.

CHAIRMAN BROWN: Okay.

DR. CLIVER: I think it is significant --

CHAIRMAN BROWN: Okay.

DR. CLIVER: -- over the longer run.

CHAIRMAN BROWN: Bob.

DR. ROHWER: I wonder if Dr. Cliver would be satisfied if the word foodborne was just struck from 1(a)? I would certainly prefer that because I don't believe that it has been established that that's how new variant cases are acquiring this disease. And then we just go with exposure.

CHAIRMAN BROWN: Yes, I thought the wording on 1(a) probably could have been -- towards the end there, you can probably scratch the entire "based on foodborne exposure to BSE in the UK" and substitute "the theoretical risk of transmitting new variant CJD from transfusions from" --

DR. ROHWER: Based on exposure.

CHAIRMAN BROWN: -- based on exposure or --

DR. ROHWER: Period.

CHAIRMAN BROWN: -- residence in the

United Kingdom. No, exposure or travel or residence to the United Kingdom. But I think we all understand that. It's just a question of words.

Yes, Peter.

DR. LURIE: It seems likely that any restriction that this committee might come up with is going to be right censored in the sense that it would be -- I'm told 1996 or some other period and include the period before that.

Now, that being the case, and particularly seeing as though people who are blood donors are disproportionately older, what this means is that any impact upon the blood supply is going to be one that will be maximal when first implemented.

And that within a period of time of some ten to 15 years, the impact of that will just kind of work its way through the population and will decrease with time until it has no impact at all. So we should look at these as really maximal impacts upon the blood supply.

CHAIRMAN BROWN: Ray.

DR. ROOS: I just wanted to give my own opinion about the whole blood versus blood derived products, which I guess maybe is a little bit of a different perspective than I think you were getting

at, Paul.

And that is, from the point of view of safety, although there may be reasons for thinking that with fractionation you're going to lower the titre and be safer, on the other hand one clearly has the -- if, in fact, the agent is in the blood, one has the danger of disseminating it far more widely with respect to the blood derived products than unit to unit transfusion, and perhaps that was one of the reasons that guided the UK to make the decisions that it did.

And so we're poised now very uncertain about what the risk is here, whether we should be guided by the data that we have, which is, of course, from classical Creutzfeldt rather than new variant. And if we worry about the risk, I think we have to take into consideration what's going to be our most dangerous action here, which I think might relate to the possibility of releasing contaminated blood derived products.

I also worry and, you know, maybe I need some education here, but does everything get fractionated? In other words, there's still, I guess, fresh frozen plasma; and, in that situation, one really doesn't have the benefit of fractionation.

Just thinking about that whole option of the -- of blood versus blood derived products and safety versus any threat to our blood supply, I wondered whether the blood bank people could educate me again.

And that is, when somebody gives blood, is it clear what that blood is going to be given to? In other words, can you ensure that units that are given might be given for whole blood or red cells or platelets and keep particular units from going into blood derived products and into this big, big vat?

And that way one might not be able to decrease the number of donors, but just redirect where those donations come from -- go to.

CHAIRMAN BROWN: Dr. Gilcher.

DR. GILCHER: I think Dr. Katz and I are going to address probably similar issues, and I really wanted to expand on the point that you had just raised.

I think question one and question two need clarification. Because the real issue in question one is should FDA recommend new deferral criteria for directly transfusible blood products. It has nothing to do with whole blood donors because it could be an apheresis platelet donor, an apheresis plasma donor.

It's a direct, transfusible product. Question 2(a) should then go to a pooled product that is used that is subsequently fractionated. That would clarify the questions.

CHAIRMAN BROWN: Could I interrupt you for just a second and ask Jay if that, in fact, is the intent of the question?

DR. EPSTEIN: That is our explicit intent.

DR. GILCHER: Because this -- and Jay, you may want to comment -- is analogous to malaria, which, in fact, was raised by the Chairperson. In malaria, if you have been potentially exposed, your plasma can, in fact, be used even in that case for direct, transfusible purposes, but certainly can be used for plasma fractionation.

Whereas, the red cells or cellular products specifically cannot if they contain red cells because that can transmit malaria. But I think the intent here is that we're talking about direct transfusible versus a pooled, subsequently fractionated product.

And the reason that's important is that on the whole blood donor side -- or let me say on the directly transfusible product side, the plasma from the donors would, in fact, be able to be fractionated.

And when you look at the amount of plasma that goes to recovered plasma fresh/frozen, and I'll give you the statistics from my center, approximately 80 percent of the 80 to 85 percent of the plasma that is derived from whole blood ends up as recovered plasma fresh/frozen.

The remainder is used as a transfusible product. So the majority of plasma derived from whole blood, at least at my center, and I suspect that's true for most of the ABC centers and probably the Red Cross as well, that plasma ends up as recovered plasma fresh/frozen, which is subsequently fractionated.

And that would not be a deferrable issue if number two were, in fact, allowed to stand.

CHAIRMAN BROWN: Right. I have a question.

Susan, you said that most of the platelets that you recover are recovered from apherese plasma. Or at least a lot of it is, huh?

DR. LEITMAN: They're not recovered. The donor is recruited and donates specifically for that purpose.

CHAIRMAN BROWN: For platelets?

DR. LEITMAN: And not only -- in my institution, 100 percent of the platelets are derived

by platelet pheresis of apheresis --

CHAIRMAN BROWN: Okay. Under those circumstances, of course, the platelets are not pooled with any other --

DR. LEITMAN: No.

CHAIRMAN BROWN: And what happens to the plasma, it goes back to the patient?

DR. LEITMAN: The pheresis product is collected in 200 to 500 ml of plasma and that's a platelet pheresis product. We don't -- most centers do not do concombinant plasma donation at the time of platelet pheresis.

CHAIRMAN BROWN: Okay, so I wanted everybody to understand this. This is a plasma pheresis. Ah, excuse me, a platelet pheresis, so to speak. It's not plasma pheresed where at least you're removing platelets and then directing the plasma to a pool.

DR. LEITMAN: That's correct.

CHAIRMAN BROWN: This is a one to one donation?

DR. LEITMAN: Platelet pheresis donation is a one type of donation.

CHAIRMAN BROWN: So the wording would -- the preferable wording, Jay, would be: Should the FDA

recommend new deferral criteria for directly transfused products?

Is that correct?

DR. EPSTEIN: Well, it's deferral of criteria for donors of blood components intended for transfusion use.

CHAIRMAN BROWN: Stan.

DR. PRUSINER: So Ray just said unpooled. That's the key word here, isn't it?

DR. EPSTEIN: Well, it isn't quite because there are transfused components that are pooled.

DR. PRUSINER: How big are the pools?

DR. EPSTEIN: They're small. They're, you know, about ten to a dozen would be typical for safe platelets.

DR. PRUSINER: Okay, so under 25?

(Laughter.)

DR. EPSTEIN: Well, I think we shouldn't get too hung up on the words. What we're talking about here in questions 1(a) and (b) are the directly transfused products. You know, whether they're given in individual units or small pools, notwithstanding.

DR. PRUSINER: Okay.

CHAIRMAN BROWN: So again, I think the words actually are important because they imply

they're important to know why ask both questions. So let's get exactly the wording that everybody can appreciate.

DR. PRUSINER: So how about, Paul, individual or as small pools, which I was saying?

CHAIRMAN BROWN: Deferral criteria for -- well, I guess all donors are individuals.

DR. PRUSINER: Right.

CHAIRMAN BROWN: For donors whose donations or who -- how do you want to word it? I know what everybody sort of understands, but I'd like to really get it down exactly.

DR. LEITMAN: I'd like to make a suggestion. It could be for components which do not undergo further processing. Pooled platelets or pooled cryoprecipitate don't undergo further processing other than some units may be frozen and then thawed.

But --

CHAIRMAN BROWN: You say pooled platelets?

DR. LEITMAN: You can get a unit of platelets from a unit of whole blood and pool six to ten such platelet units and get --

CHAIRMAN BROWN: From the same patient?

DR. LEITMAN: From different donors. A

whole blood unit can be fractionated into packed red cells, plasma and platelets.

CHAIRMAN BROWN: Yeah, you taught me that. But I thought you just said pooled platelets.

DR. LEITMAN: There's two kinds of -- there's two ways in which platelets are manufactured. One can gain the entire amount to be transfused from a single apheresis donation, or you can pool single, random donor units of platelets derived from a whole blood donation.

CHAIRMAN BROWN: So there could be several donors --

DR. LEITMAN: Up to ten.

CHAIRMAN BROWN: -- contributing a pool, and this is what you were asking. A pool of 10 or 12 donors whose platelets then are pooled.

DR. LEITMAN: The same would be true of cryoprecipitate. When one transfuses that component, there's a pool of anywhere from six to 12 units. But those products don't undergo further processing the way plasma derivatives do.

They're not fractionated, they don't go over columns, there aren't any activation steps. There aren't cuts made of the product.

So perhaps components that don't undergo

further processing would be a better way of stating it.

CHAIRMAN BROWN: Okay, and another -- yes, a question. Is it also possible historically and today, that cryoprecipitate, for example, could wind up in pools of 10,000 to 100,000. That is to say, it would be prepared from huge pools, just as, for example, IgG as opposed to ten donors?

Is cryoprecipitate a kind of special case that could have little pool or huge pool.

DR. LEITMAN: Its the cryoprecipitate when pooled, is the starting material for making pastes from which the fractionated derivatives are made, but that's not transfused as an unprocessed component. There's further processing involved.

DR. BUSCH: Still? Because in the past --

DR. LEITMAN: To make the plasma derivatives, yes.

CHAIRMAN BROWN: Yes, historically cryoprecipitate, as was given as such without further processing, huh? Paul?

DR. ROHWER: The key distinction here is that these pools, the pools that Dr. Leitman's talking about, I believe, go into one person. In other words, you pull these units together for one transfusion. So

there's only one person exposed.

They're expose to ten people, but it's the difference between having a huge pool where one person can expose thousands of people or hundreds of thousands of people or something like --

CHAIRMAN BROWN: I hear you, but that's not exactly the same thing that Jay was saying. Jay was emphasizing processing. You're emphasizing number of recipients.

Which do we want to consider, Jay?

DR. EPSTEIN: Well, --

CHAIRMAN BROWN: Which do you want to consider?

DR. EPSTEIN: I think that if we simply say deferral criteria for donors of transfusible components, it's clear enough to FDA what we're talking about because we only have two categories of donor deferral criteria, One we call whole blood, the other we call source plasma.

Now there are subsets of apheresis components for transfusion, but they follow the donor criteria for whole blood. So, you know, it's actually simpler than it seems. But I think we can correct the language just by saying new deferral criteria for donors of transfusible components, --

CHAIRMAN BROWN: Okay.

DR. EPSTEIN: -- and it will be true for that set that the products are either in single units or small pools.

CHAIRMAN BROWN: Okay. And question 2(a), how would you word that, for donors of pooled products, of what?

DR. EPSTEIN: Well, typically we would call those fractionated products. That would be another way to describe it.

CHAIRMAN BROWN: So it would be donors of --

DR. EPSTEIN: Well, I think it's correct as stated, of source plasma and recovered plasma intended for fractionation.

CHAIRMAN BROWN: Okay. I'll ask the committee if everybody understands this distinction.

Okay, Jay.

DR. EPSTEIN: Yeah, I guess the idea is that they're further manufactured into injectables. That's where the processing issue comes in. Because we do have at least one pooled product, namely solvent detergent treated plasma, which is not technically fractionated.

There's no fractionation. However, it is

further treated.

CHAIRMAN BROWN: I am clear about what you want. I think there is a contradiction in separating the second from the first. And one is that it's pooled, therefore it has the capacity to infect zillions of people.

And the other is that, despite being pooled, it's processed, so it's going to reduce all the infectivity to zero. So you've got two contradictory risk factors.

DR. EPSTEIN: Well, first of all, not all processing is equal.

CHAIRMAN BROWN: No, of course not.

DR. EPSTEIN: For example, solvent detergent and plasma has no fractionation, and yet the pools can be as much as 2,500 donors.

CHAIRMAN BROWN: Right. But your point of making two questions out of a single question --

DR. EPSTEIN: Yes.

CHAIRMAN BROWN: -- is clearly designed to make us appreciate that there is a distinction in potential risk --

DR. EPSTEIN: Yes, we --

CHAIRMAN BROWN: -- in these two situations.

DR. EPSTEIN: We reflected on the way we had framed the questions in December, and we felt that we had somewhat muddied the issue by not distinguishing for the committee that the risk/benefit equations might differ significantly.

When you're dealing with transfusion components, you have all the infectivity from the unit collection going into the recipient. Whereas, in the situation of processed products, you have large pools, you have higher risk that the infectivity would be present in the product.

On the other hand, titre is lowered. On the other hand, it goes into many more people. And layered on top of that is that the percent of donor loss would be different in the two populations as well.

Although, I think it's reasonable to speculate that the percent donor loss would be less in source plasma for any criterion that we imposed in the two settings given the younger age and lower socioeconomic status of the source plasma donors.

So, we simply felt that by having failed to make that distinction, we deprived the committee of the ability to think through the possibility of different policies in the different settings. That's

why we've split it now.

CHAIRMAN BROWN: Okay, so let's have the committee think through donors of transfusable components, right?

DR. EPSTEIN: Well, but so let me suggest --

CHAIRMAN BROWN: Yes, yes. Go ahead, Jay.

DR. EPSTEIN: -- just the wording of 2(a). For donors of source plasma and recovered plasma for further manufacture into injectable products.

DR. NELSON: I have a technical question that maybe some of the prion experts can help me with. And that is, my understanding was that this agent was fairly resistant to disinfection or treatment, and yet you're telling us that the processing will eliminate infectivity to almost zero.

And somehow, I don't -- I can't appreciate how effective is the processing with regard to removing infectivity because obviously if it's, you know, only partially effective, then we're increasing the risk by allowing pools.

On the other hand, if it's highly effective, then that's --

CHAIRMAN BROWN: Bob, why don't you produce some numbers.

DR. ROHWER: Well, the point here is that there are two ways to get rid of infectivity. One's to kill it, and the other one -- and the other way is to partition it away from your product.

And fortuitously, in the case of these agents anyway in the couple of instances in which we've been able to do this experiment, the partitioning went in such a way that the infectivity didn't go with the product.

However, there's always a denominator on that number. It depends on how much infectivity you challenge the process with to begin with. You can't claim that you removed more than you put in. And also, some steps in the process are more efficient than others and there's some question about how multiplicative those steps are.

And for technical reasons, it's not always possible to test that aspect of the fractionation over the full range of the process. So there are some uncertainties in this.

And by way of a caution, we have to realize that even though we demonstrated high levels of removal for Factor VIII, for example, for a Factor VIII process, a particular Factor VIII process that we validated, on the other hand, we know from experience

that that didn't happen in the case of HIV, otherwise we wouldn't have had this high rate of exposure of hemophiliacs to HIV.

So it's not a foregone conclusion that it will happen in every single fractionation, every single time, and it probably means that every single one of these steps ultimately has to be validated by direct testing of some sort.

And there are other caveats associated with this type of experiment -- whether the spike was appropriate, that type of thing. There are many different ways in which you can conduct it.

But all I'm trying to convey here is from the data that we have in hand today, it was very encouraging that actually there is probably a great deal of benefit at least that's derived from going through the refinement process for these products.

CHAIRMAN BROWN: Yes.

DR. PRUSINER: Bob, I would like to say that I think that, you know, the committee -- I mean, obviously when you make a statement like that, the committee is very influenced by it. And it seems to me this is very preliminary data from what you're telling us.

That's what I'm understanding. And

secondly, I want to emphasize that it's the physical state of the prions that's very important because these are proteins. They aggregate to many different size particles.

And what you choose as the spike, as you very carefully said, can influence enormously how it's cleared. And usually these particles are -- these are non-ideal particles. They're not even like HIV where we have a particle which we -- we have one HIV virus, then we have another one, and another one, and another one and they all behave the same pretty much.

That's not true with the prions. So I think that we're -- that people are getting a little false sense of security here with very preliminary data, unless you have much more data than I know about.

DR. ROHWER: Well, I would like to agree with you to the extent that we've done one experiment using one spike modality for one of these -- well, we've done four different products, but we've done one spike modality, one animal model for each one.

I think it would be much better to look at several different spike modalities in several different models, several different processes before you come to any final conclusion as to how much

security you can get from these processes.

The only thing I wanted to communicate is that compared to the crude cone fractionations which have already been published in the transfusion paper last year, these things have -- the products that are actually injected undergo a lot more refinement than the fractions that were mentioned in that paper -- that were assayed in that paper.

And we're not starting with very much infectivity to begin with. I mean, that's the other part of this equation, though that again is based on animal models and there is some question about new variant CJD.

And certainly Neil Cashman has made a very strong argument that the titers may be much, much higher in new variant. I'm not sure why he can't discount that argument, but --

CHAIRMAN BROWN: What is that argument?

DR. ROHWER: That argument -- his argument basically is that PRP RES concentrations seem to be much higher, and if infectivity directly correlates with PRP RES, then there must be more infectivity there.

CHAIRMAN BROWN: Higher where?

DR. ROHWER: In the brain, but also it's

found in RES organs -- you know, the tonsils and appendix and places where you don't find it in classical CJD.

CHAIRMAN BROWN: Would you agree that an alternative, equally plausible explanation is that this is the result of route of exposure?

DR. ROHWER: Yes.

CHAIRMAN BROWN: Larry.

DR. SCHONBERGER: Yes, I was just trying to get -- clarify what I think I heard Stan say.

Are you saying that the data that we're hearing about, the clearance of the GSS agent or other agents in the model, may not apply to new variant CJD prions? Is that what you're saying? I understand the differences in the arguments about titre and where the agent is.

But are we saying that those differences between new variant CJD and other prions are such that the clearance data should be looked at with a grain of salt?

DR. ROHWER: Well, I agree with that. All these things should be done over again using the new variant model. But again, it will be a new variant mouse model. It's not going to be a new variant monkey model or a human model simply because -- well,

it can't be a human model.

And the monkey model would just be -- it would be impossible to do this type of experiment in monkeys.

DR. PRUSINER: Yes, I think that the protein, the prion protein, the disease causing form, PRP SC in BSE is really quite different than many of the others. So it's a different strain. Because we think that strains are different confirmations of PRP SC.

And we have some recent data which is unpublished, but it has been presented at a Uri Saffire, excuse me, Mike Scott presented this data in Geneva a couple months ago, so we're trying to prepare it now for publication -- where we've been able to transmit new variant CJD into mice that express bovine PRP with incubation times of about 250 days and all of the animals get sick.

So there is, I think, a model for the future now to be able to look at this. Strangely enough, these mice have the same neuropathology as mice that receive bovine BSE prions, and much different neuropathology than these same mice that receive natural scrapie.

So I think it may be possible in the

future to get some of these answers. What I was really reacting to though -- I don't think this is really important right now. What I'm really reacting to is not being overly influenced by some early optimism that may or may not be correct that Bob Rohwer's telling us about.

I mean, I think that's all very interesting and all very encouraging, but I don't think we can make decisions based upon one time experiments. And I'm not sure that we want to do that. I think that might be a mistake.

It places a big burden on Bob Rohwer's data. And I think he would want to at least replicate it before we start making decisions based upon this kind of information.

CHAIRMAN BROWN: Yes, I don't really think anybody disagrees that we never have enough data, and this data is certainly early data. On the other hand, it seems to me early data is better than no data at all.

DR. BOLTON: Paul.

DR. PRUSINER: I don't do -- I don't think we want to debate that, but let me just say I disagree.

DR. BOLTON: Paul.

CHAIRMAN BROWN: Yes, I'm sorry.

DR. BOLTON: It seems to me that if -- this is slightly off the subject, but on the general subject. If we vote to put in deferral criteria in the first case and not in the second, aren't, in fact, we redirecting those donors from either whole blood or direct transfusable donations into pooled donations?

CHAIRMAN BROWN: Yes, that's an amusing twist. Hadn't occurred to me, but that's probably what would happen.

DR. BOLTON: Then I guess the question is: Is that acceptable to the blood banks, and is that a good outcome?

DR. NELSON: I said that's the reason for my question.

CHAIRMAN BROWN: We have a comment here.

DR. EWENSTEIN: Well, I was going to ask just a little bit more on the fractionation procedure just as a point of information.

Do you have mass balance at this point on those experiments? And also, you know, sort of -- it begs the question in the commercial operation: Where are these infectious particles now? I mean, they're still on the cow?

DR. ROHWER: That's an extremely

perceptive question. We do not have mass balance, and I don't believe we're ever going to get mass balance using these types of experiments and these types of models simply because to do the experiment on the scale on which you have to do it in order to get a mass balance would be prohibitively grandiose.

And so we're only going to get a glimpse of what's going on in these things.

No, these experiments will -- I really don't think there's much hope for them ever meeting the same standard that would be applied to a conventional virus. I don't think -- unless we can come up with an in vitro assay or something like that that allows us to actually do the assays on the same kind of scale that you can do them for in vitro work, I don't think that's going to happen.

CHAIRMAN BROWN: Yes.

MR. COMER: Thank you, Chairman. I just thought it might be worth informing the committee that I was at a meeting of the World College of Physicians in Edinburgh about two weeks ago and the Scottish National Blood Service were reporting a series of experiments that they have been doing on clearance factors for fractionation.

I don't have the paper with me and it was

at a meeting, not a published paper, but they are doing quite an extensive series of work, again obviously using mass model, but I believe getting very similar results to those that Bob's reporting.

So there are at least other data that support the -- we're getting similar sorts of results. Six full log clearances for many of the processes within the fractionation area.

CHAIRMAN BROWN: One further point is that in the paper that was published that Bob referred to in which a spiking experiment was done and a parallel experiment was done using an endogenously infected model, one could have predicted the other, which is just a little point in favor of at least that spike being a pretty good spike.

That spike happened to be intact, infected brain cells. And the distribution was very similar to that found in endogenously infected mice -- that is, mice that weren't spiked, but the infectivity was within the cell -- excuse me, within the blood naturally.

Yes, Ray.

DR. ROOS: I wonder whether that study was done on BSE and new variant or another one of the spongiform encephalopathies?

MR. COMER: No, it was a scrapie mass model.

DR. ROOS: Okay. Because I just want to mention we have run into problems in the past with the spongiform encephalopathies with pooled material such as the dura mater, lyadura event and growth hormone.

We've also had problems with the unit to unit approach, obviously, but the toll there is far less. And I do think the data is good. And in fact, I think that the data that we have from Paul and Bob have clearly clarified a lot of things.

And I don't think we would be struggling with some of the issues here if we hadn't had that data -- that is, that the agent is in blood, and that even the intravenous route works, and that this is a cause for problems.

But I am a little cautious about the issue of the fact that it isn't in -- it isn't the new variant agent that we're dealing with and that some of the rules may be different.

CHAIRMAN BROWN: Well, this is exactly why we're here today. Dr. Satcher and the other groups have already decided that this is not worth significant worry with respect to classical CJD, and that new variant was an unknown.

And so that's why we're considering specifically new variant because we don't have information specifically on it. I mean, everything we don't have information on becomes a subject for this committee.

(Laughter.)

DR. McCULLOUGH: I'd like to go back to the two different groups of donors. I think if the committee made different recommendations for the plasma donors versus the transfusible product donors, it seems unlikely to me that we would divert donors from one group to the other.

They're generally different -- fundamentally different groups of donors, and I think there's very little cross over back and forth between those groups is point number one. And point number two, that even if blood centers decided to start to generate most of their plasma for fractionation by plasma pheresis, they really aren't set up to do that.

The equipment is limited and the economics are marginal with volunteer donors. And so I think that the concern that we might divert donors from one group to the other is probably not a practical one.

CHAIRMAN BROWN: Dr. Epstein.

DR. EPSTEIN: Well, two comments, first on

this point. To prevent diversion, what we would do or could do is to recommend that if a donor of blood components for transfusion is identified to have this risk, that that donor's plasma not be distributed as recovered plasma for fractionation.

That could operate coincident with a system where source plasma donors aren't asked that question. So you'd have no diversion, but you'd still have two different systems operating. And I think that's the way we would reconcile it to prevent, you know, diversion.

Back to the point of consistency among studies of partition during fractionation. FDA has seen a second complete data set from one of the fractionators with experiments that were designed similar to the ones that Drs. Brown and Rohwer organized and those data were entirely consistent.

They, of course, suffer from similar limitations. As Dr. Prusiner said, you're using a particular type of spike obtained in a particular way. It's artificial compared to natural infection.

But still, if you look at the logs clearance at highly specified steps of processing, the consistency was near absolute in the two different experiments. Now those data are not public.

CHAIRMAN BROWN: Bob.

DR. ROHWER: But I would also like to make perfectly clear that I would not propose intentionally ever challenging the plasma fractionation with blood from new variant CJD cases just because you didn't know what else to do with it.

That is not my intent. It's just that there is an additional margin for error in any refinement process or margin of safety. Whether it's absolute or not is still open to additional verification.

CHAIRMAN BROWN: Yes.

DR. EWENSTEIN: I was wondering whether there were other data, the IV Ig processing as well, the other high risk recipient group.

DR. ROHWER: There is for the Nietschman Kissler process. We've presented that several times now and we're preparing that for publication. This is a process that's used by the Swiss Red Cross for making IV Ig.

And again, we saw, oh, four to six logs of removal at several steps in that process.

CHAIRMAN BROWN: The committee seems to have run out of gas on this rather early. I hope not.

DR. LEITMAN: I have a different question.

CHAIRMAN BROWN: Yes. I'm sorry, where are we?

DR. LEITMAN: I'm over here, Dr. Brown.

CHAIRMAN BROWN: Oh, sorry.

DR. LEITMAN: We seem to be extrapolating the partitioning data of classical CJD -- the agent of classical CJD to the agent of new variant CJD. That may or may not be okay.

I'd like to ask Dr. Prusiner if we can at all extrapolate the lack of transmissibility through blood components of classical CJD agent to new variant?

DR. PRUSINER: I don't know that I'm qualified to answer this. I can only tell you that the little bit of work that we've done now on new variant CJD says that it is a dramatically different strain of prion. That means that the confirmation of PRP scrapie is dramatically different than anything else we've studied.

So let me give you an example. We've looked at 40 different cases of sporadic CJD, and we know that there's several different confirmations there at least. And all of these are transmissible in about 200 days to either mice that have a human PRP gene or have a chimeric mouse human PRP gene.

If you look at new variant CJD, it takes more than 500 days and only about 60 percent of the animals get sick. Now, as I said before, if we take new variant CJD and we passage it into a mouse that expresses a bovine PRP gene on a null background, then all the mice are getting sick in 240 days.

The piece of data I don't have that you want is you want to know if I take sporadic CJD or familial CJD cases and passage those into mice with a bovine PRP gene, do they get sick? And the answer is I don't know yet.

But clearly, when we look at mice with human and chimeric mouse human PRP genes and we inoculate those with new variant CJD, the mice are very resistent. And there's a little bit of data from John Collinge, which has been published, which is in agreement with those findings.

Then if we take this and inoculate it -- these inocula from new variant CJD, inject them into mice with a bovine PRP transgene, they get sick. So that says that it's dramatically different than anything else that we've seen that comes from humans.

CHAIRMAN BROWN: But what I think Susan really wants to know is if you took new variant CJD and inoculated it into humanized mice, and then took

the blood from those mice and put it into a further group of humanized mice, would it transmit disease as opposed to the bovine transgenic or any of the other transgenics?

DR. PRUSINER: And the answer is I don't know. But I think there's another lesson. I mean, I agree that the work that you and Bob have published is most interesting. But there have been a lot of studies where people have taken blood -- so these are mice that are intracerebrally or hamsters intracerebrally inoculated.

And then people have gone to try to recover infectivity from various fractions or from whole blood, and this is exceedingly hard to do. I suspect that there are many, many more negative results out there where people were unable to do this than positive ones.

And the negative ones, of course, don't get published. In our own experience, which is not huge, we've had very non-reproducible data, which is why we've never published any of it on the recovery of prions from blood.

We haven't done yet the experiment you suggest, Paul. I mean, we will do this. But I feel very uncomfortable about the assays for prions in

blood. I don't know what's going on. I don't understand. There's a piece of scientific information that's missing there. It's a methodology.

CHAIRMAN BROWN: What specifically?

DR. PRUSINER: Well, the fact that we get variable results. I'll just give you very quickly our own experience for the congressional record. We did an experiment a number of years ago, and this dates back about three years, with hamsters.

And we isolated white cells and plasma, whole blood. And we inoculated white cells into additional hamsters. And these were -- the plasma was taken from animals that had just showed the first signs of clinical illness.

And the titers were fairly high. And when we corrected this per gram of protein, we had about 10^4 infectious units per gram of protein. So we were like three logs or two logs below brain. And then we tried to repeat this study.

We did a very large study taking samples at various times after intracerebral inoculation in the hamster, and then we went through this series of bioassays trying to repeat what we had done and we never found any infectivity the next time.

And I don't know what the difference is

between the first experiment and the second experiment. And then we did a series of experiments to see whether or not the feicol that we were using or the percol we were using to separate out the white cells or the edta or the citrate -- if any of these were important, and we never figured this out.

We saw if we took brain extracts and we added these various chemicals to them, we saw some small decrements in infectivity occasionally, but nothing consistent that would explain why we couldn't reproduce our data.

So I feel very uncomfortable that I don't understand this, and so I always look at these blood studies with big question marks. And if you go through an make a table -- I think Bob Rohwer's done this, or you've done it, where you compile all that's available.

And I know Hank Barron, who is here -- or was here -- he's done this. Maybe he'd like to speak to this. But you get -- you see that the results are not totally consistent, and I don't understand this. I'm concerned.

CHAIRMAN BROWN: Well, if I had experiments that you describe, I'd be uncomfortable as well.

(Laughter.)

CHAIRMAN BROWN: That in riposte to your comment about being interesting, which I always interpret from you as being as damning with faint praise.

I think the explanation for the inconstancy and variability is that you're probably dealing at threshold levels of infectivity. At least I think that's a major contributing factor. I think it's not worth discussing at length, but I will add what has been implied, but not clearly stated, that we have replicated now the experiments in mice two more times with consistent results.

Three separate experiments. So I'm much more comfortable with that set of experiments than you were with the hamsters. I will also say, in favor of variability, that our results, in certain respects, are consistent with Bob's work with hamsters.

In certain other respects, they differ. It would be very nice to have the hamster work and the mouse work consistent right down the line. They are consistent in terms of the level of infectivity that Bob is finding in hamster blood and I'm finding in mouse blood.

And incidentally, the mouse model, for

those of you who -- is a human strain of TSE. It happens to be from Gerschman Sträussler and it's a mouse adapted strain. Bob is using the typical ~~s~~crapie, high titre, 263K strain.

Irrespective of the two strains, the level of infectivity in the blood is consistent. It's ten to 20 infectious units per ml of blood. Where we differ dramatically is that in the mouse model, IV transmissions are fairly commonplace.

They're not as commonplace as intracerebral transmissions when you put blood in the brain, but we got a lot more than we bargained for. Whereas, Bob's hamster experiments, he has, I guess, still just a single transmission out of somewhere of 50 -- between 50 and 100 attempts.

Granted, there are certain technical differences, but that's an illustration of the fact that two different rodent models can, in fact, differ. And we're not going to solve that today. I mean, that's biology.

Yes.

DR. BELAY: How do you compare the clearance process of the different fractionation states? Is there more clearance at the first -- at the last fractionation state compared with the first

one, for example?

CHAIRMAN BROWN: Well, I can talk about just a simple Cohn fractionation, yes. It's a cumulative thing. I mean, each precipitation builds on the previous precipitation. Cryoprecipitation leaves a precipitate in the supernate.

The supernate is then reprecipitated and you get fraction one, two, three. It's a little more complicated than that. By the time you get down to four or five precipitations and albumin, you'll just about run out of infectivity even when you started with ten to 20 infectious units per ml.

That's just a physical following of this infectious agent with precipitate. And that's consistent. We know that years and years and years of all kinds of experiments that have nothing to do with blood have consistently shown that precipitation tends to take out this infectious agent.

Yes, Blaine.

DR. HOLLINGER: I think you bring to mind one of the concerns that I always have about using mouse adapted models and other things, which may not be equivalent to natural disease. It could be concentrations of virus much more than what we see naturally.

And, I mean, we see this with albumin, which was supposed to be very -- which is very safe. But you can overwhelm the system by putting in lots and huge concentrations of virus and end up with an albumin product that will transmit hepatitis B, for example.

Has anyone, Paul -- anyone here. Has anyone done any experiment -- I mean, the BSE problem has been down now around since 19, what, '83 and patients have been around since maybe '93 or '94. Has anyone done any experiments with just calves that are infected taking whole blood from calves and infecting other calves?

They don't have to come from -- they can be calves from another source where there would not be any disease, but infected those to see about transmission of this disease through whole blood. It seems like that's a natural experiment that would be relatively easy to do.

CHAIRMAN BROWN: Not easy to do. It is a natural experiment. It's on test, as I understand it, at Weybridge in the United Kingdom. And the calves, so inoculated, are still on test. Calf blood has been injected into mice so that you've got a species barrier.

That hasn't worked. And the calf experiment is still incomplete.

If there's anybody from the UK that has more up to date or correct information, that's as far as I know. So yeah, you're right. I mean, that was an obvious thing to do.

One of the problems is people didn't get interested in blood until a little bit later than they should have. And as you know, in this country, although we've been interested in a timely way, we've bene unable, due to the prudence of the USDA, to work with it.

Bob.

DR. ROHWER: Paul, it seems to me that the issue before us is to decide first whether we want to make a distinction between blood for use in directly transfusible products versus pooled products. And then if we decide we're not going to make that distinction, then we can move on.

CHAIRMAN BROWN: Is the committee -- Ray. And then after you say something, I'll ask the committee if they're ready to take a vote on whether or not we recombine, in spite of Jay's best efforts, both questions into a single question.

Ray.

DR. ROOS: I wasn't -- we've seen several times this figure that Steve Nightingale showed of the issue of the dangers to our blood supply and the risks. And I got a little confused with respect to transfusible components versus pooled products and how that figure related to those two different groups.

You know, we've spoken a little bit about issues related to safety of those two groups, the risk of those two groups, but I'm not quite clear about the availability and whether the -- whether we should lump them together.

CHAIRMAN BROWN: Yes, that's a good point.

Marian, why don't you defend -- or not defend, but clarify that. The data that went into your figure is based on what group?

MS. SULLIVAN: Based on whole blood collections, whole blood and red cell supply and demand. And of course, the products -- our data include -- our other data include components that are made from those whole blood donations and also pheresis -- specific pheresis donations.

But the figure --

CHAIRMAN BROWN: But it's based on whole blood --

MS. SULLIVAN: -- that we're talking about

is whole blood and red cells.

CHAIRMAN BROWN: -- donors rather than apheresis donors?

MS. SULLIVAN: Usually considered to be a good indicator of available supply.

CHAIRMAN BROWN: No, but is that correct? That is, this data is based on a population of whole blood donors?

MS. SULLIVAN: That's correct.

DR. ROOS: So what can I derive with respect to these pooled products? Do we know about their availability and what's anticipated for the year 2000?

MR. REILLY: Jim Reilly with ABRA.

We didn't publish the way that Marian did, but we recently collected some data which gives us some insight, but not absolute, definitive numbers on supply. First, there is, as probably everyone is already aware, a fairly substantial shortage of immunoglobulin.

Most of that is a bottle neck at the plant, but there is a very delicate supply and balance between source plasma supply and the fractionation capacity. Last year our estimates are that we were down about 13 percent overall.

And so for this year, it's just anecdotal, but it would suggest that we are probably down a little bit to even with last year. So we are in a very precarious balance and supply situation right now.

CHAIRMAN BROWN: Jay.

DR. EPSTEIN: Well, Bob, if I could comment though, is it not true that only half of the source plasma collected ends up in U.S. products? In other words, roughly -- there's roughly twice as much plasma is collected for fractionation than is utilized for U.S. products.

Worldwide, I recognize that there's still a shortage and that, you know, you meet needs of international customers. But still it remains true that the U.S. supply of plasma for fractionation is twofold greater than the U.S. consumption for U.S. use.

MR. REILLY: Yes. I don't recall off the top of my head whether it's half, but it is clearly in excess, yes.

DR. EPSTEIN: But vastly in excess compared with the situation of collection versus demand for --

MR. REILLY: Yes, Jay.

DR. EPSTEIN: -- blood component.

CHAIRMAN BROWN: At the microphone and then Dr. Sayers.

DR. DAVEY: This is a comment about recovered plasma or whole blood derived plasma. All of that material is used for U.S. consumption essentially. And I think if we are considering a deferral for that particular material that's going for further manufacture, the committee should consider the problem of post donation information.

We, at least in the Red Cross, often hear back from our donors days or weeks after a donation that there's some information that they forgot to tell us or whatever that impacts on how we handle those products that have already been obtained and perhaps sent for further manufacture.

So we will hear from donors that -- of the millions that we have, that gee, I forgot I was in the Army in England for a year or something or other. And we are going to have to deal with that information then in terms of market withdrawals.

Perhaps that plasma has gone into a big pool that has been manufactured into Factor VIII, IV Ig, whatever, material that's in very short supply. So post donation information has to be considered,

especially with its impact on the blood supply.

CHAIRMAN BROWN: Jay.

DR. EPSTEIN: Well, the committee voted in December that there should not be derivative withdrawals based on post donation information related to residence or travel in the UK, and the FDA has accepted that recommendation.

So I don't think that scenario presents itself.

CHAIRMAN BROWN: Dr. Sayers.

DR. SAYERS: Thanks, Paul.

I just wanted to say something about availability now that we've gone onto that. And it looks as if, judging by the way some of the conversation has gone, that the committee might end up with trying to make a decision about how much additional deferrable is tolerable against the background of this relative inelasticity of the nation's blood supply.

And I think cynics could reasonably argue that that's just making some sort of token concession to this issue. But I'd hate the committee to come up with some decision about what is tolerable in terms of a deferral rate if they assume that some of the other comments about the availability of additional donors

are indeed true.

And the comments that I'm referring to are the fact that one could be pardoned for thinking that the first time donor who is now a lapsed donor is somebody that could easily make good for any additional deferral that CJD criteria would superimpose on the nation's blood supply.

I mean, that idea flies in the face of what has been an incredibly aggressive attempt to recruit former donors, lapsed donors, recent donors, donors of any marking whatsoever. Community blood programs' attempts to recruit have been, as I say, aggressive.

What we're understanding is that part of the reason why those attempts are failing and part of the reasons why we see those two lines on that graph that Steve Nightingale intersecting -- part of the reason for that is that the whole donation process has become so alienating.

I mean, donors now find themselves spending twice as long during the donation process as they spent as recently as five years ago. Donors find themselves being given health information history which they very correctly perceive to be in total contradistinction to how they feel about themselves.

Donors find themselves being deposed. They find themselves involved in lawsuits. They find themselves being sent off to their physician and then incurring costs in terms of understanding what the health implications for some of the information is.

And I heard you say, Paul, that this is an issue of education. It certainly is. But it's not been against the background the blood programs have been less than resolute in attempting to apply this education.

The problem really boils down to this: when you tell a donor who has been deferred for any number of a whole host of reasons tied up with non-specificity that he or she can no longer donate, but you give that individual the reassurance that you're satisfied that he or she is healthy, when that donor comes back with an astute comment like "well, if I really am healthy, Doctor, why can't I donate," and you have no answer to that, then no amount of education is really going to be successful.

So I'd hate to think that this is going to come down to a decision about how many more donors can we defer, assuming that it's going to be easy to make up that deficit.

CHAIRMAN BROWN: Yes, Stan.

DR. PRUSINER: I'm really uncomfortable with these arguments that you just made. In fact, I'm exceedingly uncomfortable because to end the conversation with the patient by saying what you just said is just not accurate.

There are large numbers of answers. I mean, we went through this at the University of California and a whole set of discussions with a committee to try to set a policy. And the fact is that there's a lot of scientific information, and then there are a lot of clear unknowns.

And the unknowns have to be clearly stated to the patient. And for you to stand there and say what you just said I think is unfair to the committee, it's unfair to the population of the country, and it's really not accurate.

CHAIRMAN BROWN: We're warming to the task now.

DR. SAYERS: Let me blow some air on the embers, then.

(Laughter.)

DR. SAYERS: I'm mindful of what Dr. Tabor had to say about how we should accurately define "donors." And as an immigrant to this country from the UK, I think I can reasonably define myself as a

variant UK donor.

That aside, would that the donors that we deal with whose health history is significantly impacted by what is tantamount to the largest public health exercise in the world -- I mean, 40,000 people a day get tested by six or seven markers of infectious disease.

They get tested for markers of infectious disease like HTLV that the American College of Obstetricians and Gynecologists doesn't even regard as something which should be part of a pregnant individual's antenatal workup. And yet, we have to give those donors, if they're reactive in that assay, advice about whether they should be breastfeeding or not.

Now, these are not responsibilities that we have taken willingly or enthusiastically, but our issue really is that the donor's understanding -- his or her perception of what constitutes good health -- is not a perception based on the incredible insights and understandings that the pooled members of this group can represent.

To say that my remarks do a disservice to the donors, or to the committee, rather, without elaborating on it, I would have to say that any

deferral of donors, for reasons that are not rooted in science and for reasons that can securely steer us away from a further erosion of the blood supply, any decisions made on that basis are going to be a disservice to the three or four million transfusion recipients that we have to be concerned of annually.

CHAIRMAN BROWN: Okay. That's a pro and con.

Before we have any further discussion, I would like to ask the committee if they would be prepared to vote on the following question. Is our current knowledge insufficient to permit us to vote separately on questions 1 and 2? And is that -- I think this is the sense of one of the avenues of discussion that has occurred this afternoon.

Do we really know enough to be able to make this distinction, to be able to distinguish between risks from question 1 and question 2? So would the committee like to vote on whether, once again, to combine these into a single consideration of donor deferral -- blood donor deferral? All bets off, just no further distinction than that? Yes?

DR. BURKE: My question bears directly on that, and it's for Jay. And could you please review any precedents that there are for deferrals that are

-- where that's differentiated already, where there are FDA precedents for taking one class of donors and saying they're deferred for exactly the same age and then not deferring them in another donation setting.

DR. EPSTEIN: Yes. We currently screen donors of transfusable components for the anti-core marker for hepatitis B. We do not screen source plasma donors for manufacture of derivatives for that marker. We currently screen donors of transfusable components for antibodies to HTLV. We do not screen source plasma donors for markers of HTLV.

We do recommend, however, that if recovered plasma is obtained from an HTLV positive donor that it not be sent for fractionation. However, we do not prevent releasing anti-core positive plasma as recovered plasma for fractionation.

And then, as was mentioned earlier, we defer donors of transfusable components if they have risk factors for malaria, and we do not screen them, nor do we interdict recovered plasma based on risk factors for malaria.

DR. BURKE: So in every case where there is this exception, it's on the assumption that the agent poses less of a risk and is inactive -- and can be inactivated in the pools.

DR. EPSTEIN: Absolutely. That has always been the guiding principle.

DR. BURKE: So the issue of having it as a pool, and, therefore, putting a greater number of people at risk is not a precedent so far.

DR. EPSTEIN: Well, as I tried to say earlier, we could avoid that situation by adopting the posture we have for HTLV, which is that if you're screening the donor of transfusable components, and you have a risk factor based on exposure in the UK, that you would then interdict the recovered plasma. So you wouldn't fractionate it or transfuse it.

So we don't have to cause a situation where we have divergence. But at the same time, you could have the policy where you are not screening the source plasma donor for that history.

CHAIRMAN BROWN: Let me, Blaine, say something, because the committee is starting to go around in circles, which we often do at these meetings at some point in the afternoon.

I think we have imperfect -- very imperfect scientific knowledge on which to make any decision we are going to make today. We do have a couple of pieces of information that bear on this distinction.

In animal models -- rodent models -- we know that most of the infectivity is in the white cell component and comparatively less is in plasma. In rodent models, we know that it takes at least five times more infectivity to produce an infection when given IV than when given IC; that is, intracerebral. This means that a dilution effect in pooling can operate.

Yes, go ahead.

DR. PRUSINER: Did you say five times or 10^5 times?

CHAIRMAN BROWN: No, no. Five. Five. Five.

DR. PRUSINER: All right.

CHAIRMAN BROWN: Just five. Not very much but enough so that when you do the arithmetic you find that the likelihood of having five intracerebral infectious units in a single vial of product is very low, much -- I mean, phenomenally lower than if you had just one infectious unit -- was enough.

So pooling and its dilution effect, with respect to getting five IC infectious units together in a single dose, is a real thing and it's a safeguard. On the other hand, it is in rodents. It has only been demonstrated twice, two independent

experiments. And it's in a model which is not new variant CJD.

I mean, this is where I'm talking about imperfect. We go two or three steps back.

Robert?

DR. ROHWER: Paul, I would encourage us not to invoke the pooling argument because I strongly disagree with it and do not feel that that's likely to be playing a role. And we could go on and on about it, and try to resolve it here, but it is a technical issue that it is possible to take two different positions on it. And I don't think it's possible to resolve it here, so I don't think it should be invoked.

I think we should consider the -- it is a worst case situation that if you take a 10^4 infectious units and disperse them into a pool, you have the potential of distributing that to 10^4 individuals ultimately in separate product units.

And I'd rather work from that point of view. If there's any value or any safety that can be taken from plasma, it's from the refinement process itself. But I do agree with Stan that we've only looked at a couple of different processes by a couple of different models. It's not a closed situation.

And I certainly myself would not be in favor of invoking that as a reason for making this choice. I think we'd have -- it's more important to look at this from the standpoint -- really, from the same standpoint that -- well, actually, the British didn't use that rationale, but we all thought they did at first. But the idea that the directly transfusable products expose far fewer people than pools may expose and make the decision on that basis.

CHAIRMAN BROWN: Well, it's just -- you know, it's --

DR. ROHWER: There's no distinction.

CHAIRMAN BROWN: Yeah. Right. I don't disagree that it's arguable. I don't know how you argue against data but you do. My point then goes back to the original proposition, let's assume we don't know a damn thing.

You're telling me that the pool dilution argument is arguable. The partitioning of infectivity in blood is arguable. The relevance of spiking experiments is arguable. The appropriateness of rodent models is arguable. Do we have enough information to warrant considering questions 1 and 2 separately? That's the first question. Can we take a vote on that?

If people think we have enough information to consider question 1 apart from question 2, let's get on with it. If we don't, let's combine them and simplify our lives.

DR. ROHWER: Right.

DR. ROOS: Well, the two things we know is, as Bob says, if there's 10^4 infectious units in the pool, we have the possibility of infecting a thousand people versus 10^4 in one sample. And the other thing that I think --

CHAIRMAN BROWN: That's what I argued with. But go ahead.

DR. ROOS: No. Really, the infectious unit is defined by an intercerebral infectious unit. If you need five of them together when you give it intravascularly, then you're not going to get it if you dilute out to one in a million. You'll never get five in one vial. Well, I --

CHAIRMAN BROWN: That's what we don't want to discuss here.

DR. ROOS: Okay. The second thing that I -- well, there are issues related to those issues and the different routes. I guess the other thing that I think I heard was -- from Jay was that, in fact, we have enough pooled plasma derived products in the

United States -- that is, that the issue of risk of shortage in the United States seems not to be present in the pool derived products but certainly is present in the transfusable components. There's a different issue of availability of these two that I think also makes them different.

CHAIRMAN BROWN: Okay. That's a good point.

DR. LEITMAN: Could I object to that? There is a great difficult getting IV Ig. No matter what the manufacturers may say, we've had to cancel protocols because our pharmacy is unable to get IV Ig for new experimental IND -- you know, IRB approved indications. You can barely get it for the approved indications.

And if you speak to patients and consumers who use the IV Ig, such as those on the BPAC Committee, they are very concerned about any additional deferrals on donors based on that.

CHAIRMAN BROWN: Is this going to be passionate, Larry?

DR. SCHONBERGER: Yes. I was just going to suggest that we keep the issues separate. I think that each of these questions raise different issues. They do not necessarily mean that an individual would

have to change the criteria for 1A versus 2A. But the vogue will be based on different issues that they're weighing. And I think we could move on and just --

CHAIRMAN BROWN: Okay.

DR. SCHONBERGER: -- proceed to go with the way Jay had had it.

CHAIRMAN BROWN: Okay. Barbara, we'll hear from you, and then we will, in fact, take a vote on 1A and go on from there.

MS. HARRELL: Okay. As a consumer representative, I've sat here and I've listened because I tried to -- I'm probably the only non-scientist on the panel. And I'd just ask my learned colleague a question.

CHAIRMAN BROWN: Which one?

MS. HARRELL: Is there a --

(Laughter.)

CHAIRMAN BROWN: No. I'm -- do you mean all of us?

MS. HARRELL: Just this one, right here.

CHAIRMAN BROWN: Oh. Oh, okay.

(Laughter.)

CHAIRMAN BROWN: I wasn't being smart. I just didn't know which one you were talking about.

(Laughter.)

CHAIRMAN BROWN: Go ahead.

MS. HARRELL: Well, I asked him the question, was there a deferral -- was there deferral criteria for blood donors for classic CJD for people who have either resided or visited the UK.

CHAIRMAN BROWN: I'm sorry. Repeat that, the question.

MS. HARRELL: Is there a deferral policy for blood donors to attempt to reduce the risk of transmitting classic CJD for people who either resided or visited the UK?

DR. SCHONBERGER: The answer is no.

MS. HARRELL: And if there is no risk, if we think that there is no risk of transmitting the whatever to -- for CJD, what makes this different, for new variant CJD much different?

CHAIRMAN BROWN: That's the first time, Stan, you'll ever hear of prion referred to as a whatever.

(Laughter.)

CHAIRMAN BROWN: I mean, I've heard it referred to as a lot of different things. I'm --

DR. PRUSINER: You've said that many times, Paul.

(Laughter.)

CHAIRMAN BROWN: It may be that --

DR. PRUSINER: Is that in the Congressional Record?

CHAIRMAN BROWN: The issue is not about sporadic CJD. That is the issue we can sort of generically say CJD. Presumably, if the blood from a patient with new variant CJD were infectious, the disease that it would transmit would be new variant CJD. So it's not --

MS. HARRELL: Okay. So CJD is not transmitted through the blood is what you're saying?

CHAIRMAN BROWN: We have no evidence from looking at populations that that has ever happened. The question is: since we know it can happen when we use experimental models of CJD, we can take CJD blood from one animal and produce the disease in another animal.

So there is the "theoretical possibility" that this might also happen in humans, particularly with a different strain of the disease, which new variant is, about which we don't know a whole lot. That's the question.

DR. SCHONBERGER: Isn't the answer to her question that the incidence of CJD, REDS, classic CJD, is not influenced by whether or not you've lived in

the UK between 1980 and 1996 --

CHAIRMAN BROWN: Yes.

DR. SCHONBERGER: -- but the incidence of new variant CJD is?

CHAIRMAN BROWN: Yes, 40-love.

(Laughter.)

CHAIRMAN BROWN: Stan?

DR. PRUSINER: Maybe, Paul, it would be useful for you or someone else to just summarize what went on in December, the background for this, why new variant CJD may or may not pose a risk to the blood supply, because this all went on in the last meeting.

We had all of these consultants come and talk about this, and maybe there are other people at the table who really aren't up to speed on this, because this is really the background piece of information upon which this whole discussion is based.

MS. HARRELL: I was here. I've just forgotten. That's all.

(Laughter.)

DR. PRUSINER: That's fair.

(Laughter.)

MS. HARRELL: But the other thing is that there has been discussion back and forth, and we really don't have enough data to -- I don't think to

make a decision. But I do go along with the Canadian -- Ms. Chan's presentation that in light of -- without having the data, that you take a conservative approach in that you do not wait for the scientific certainty. That as a representative for the community, or for the consumer, that they want to reduce their risk as close to zero as possible.

As far as it affecting the blood supply, I think that that is something that may be totally separate that we will have to consider. But first, we don't want anything to come into the country that is not already here. And if there's something that we can do, then we should do that.

CHAIRMAN BROWN: Okay, Barbara. I think without further ado -- we're really running out of time, Susan.

DR. LEITMAN: Let me return to the apheresis donor issue. There is some level of decrease in -- or deferral of the whole blood donor population that the American blood supply will tolerate. Maybe that's half a percent, one percent, 1.5 percent, but it probably could be tolerated.

I don't know what the apheresis donor population would tolerate, but we just heard from Dr. Gilcher earlier that that might be as high as a four

to five percent or higher deferral of repeat donors. Is that enough of a problem that this committee thinks it might need more information on that population of donors of transfusable products before it started making deferrals based on time spent in another country?

CHAIRMAN BROWN: Is the committee ready to vote on question 1A? Bear in mind that the vote on question 1A implies an answer to question 1B, and that if you -- if you recommend that the FDA recommend new deferral criteria, you are automatically obliged to recommend what those criteria should be.

DR. ROHWER: Paul?

CHAIRMAN BROWN: Yes.

DR. ROHWER: I would like to raise one other point before we vote on this, and it's to a remark that Barbara has just made here about getting as close to zero risk as possible. I don't think we should fool ourselves. Whatever we come up with here this afternoon is not going to be anywhere even close to zero risk reduction or zero exposure reduction.

It could go all the way to zero in terms of geographical exposure. We're talking about 20, 30 percent deferrals, which I don't think is likely to happen.

And in any case, no matter what we come up with, we have to recognize that whatever policy we put in, whether tomorrow, next week, or next month, we've been living without that policy for the last 19 years of exposure to this agent. From 1980 to 1999, the period that was in the REDS study travel questionnaire earlier, that's a 19-year period where we have already assumed that exposure.

We have already had that exposure. We've already had those donations. We've already had people who have received blood from those donations donating again. That has already taken place.

What we're doing here is mitigating further exposure to some extent, and to what extent that is we have no idea, really. And so I don't think we should -- I think we have to keep that in mind. The advocacy of what we're doing here is a little bit questionable in my mind. It seems to me that if we can do something that has very little cost attached to it, we should, but that is the proviso.

CHAIRMAN BROWN: Okay. Were you finished or -- yeah.

Dean, I just want to say that you could argue the same way, and you're right. But someone who smoked 20 years and is told, "You've smoked 20 years;

there's no real rationale for you stopping," I think there is.

DR. ROHWER: I agree with that. And I would like to add one other thing, and that is that I have proposed at various times before this committee and various committees that one way to build a firewall between us and our prior exposure, which has the same attributes as the feed ban that was so effective in bringing the -- turning the BSE epidemic around, is to defer donors who have already been exposed, i.e. people who have already received blood and blood products.

And the problem with that is I have not been able to get a good sense that that is at all practical. But it is something which I would hope that we could consider at greater length at some time.

CHAIRMAN BROWN: The committee should bear in mind that we have exactly two minutes, if we want to remain on schedule, to take votes on 1A, 1B, 2B, and 2A.

Dean?

DR. CLIVER: One thing I'm not hearing is when we talk about the impact of deferral of, for example, 2A, we can choose to minimize risk, but you've got to be first. And the UK was first. They

have already made their decision on this 2A question. In part, I suspect, why we're processing a lot of plasma for -- not to be used in the United States is we're already being outbid for plasma products that are going to the UK.

Now, are we prepared to cut off our supply, or diminish our supply, and hope we can outbid them to bring our own stuff back or keep it? This is -- I think we're not supposed to think about economics. But all the same, if you're going to be very conservative on these points, it pays to be the first one to --

CHAIRMAN BROWN: Yes. No, I think the FDA has given us carte blanche to consider anything we want to on this particular issue -- economics, tradeoffs, risks.

Does the committee want to punt, or do they want to vote? The Chair is finding it a little difficult to refocus this and decide exactly what we should do to try and satisfy the legitimate demands of the FDA for our advice. Yes?

DR. PRUSINER: So why don't I just preempt this and say I'd like to make a motion that we vote on 1A.

CHAIRMAN BROWN: Well, that's what I was

going to suggest. Is that -- is the committee satisfied to finally take a vote on this issue, imperfect as the basis for our judgments --

DR. LEITMAN: I have one last comment. I've heard Jay Epstein say that there will be no product recall. So whether there is post-donation information, or whether a donor comes in the next donation and then gives the information because they're asked for the first time whether they have ever been in England and they say that they lived in England for half their life, for example.

But the previous products or fractionated products are not recalled. So if they're not recalled, it's hypocritical. The whole policy is hypocritical. You prospectively defer, but you have vast amount of product, especially fractionated product, derived from the same donor that you don't recall.

If you have such a hypocritical policy, then my conclusion from that is that this is simply a gesture, a public relations gesture, without any scientific data or any perception of real risk by anybody sitting here, without making an across-the-board removal of product from such donors.

CHAIRMAN BROWN: I think "hypocritical"

probably is too strong a word. It may not be fully logically consistent.

DR. LEITMAN: Illogical is --

CHAIRMAN BROWN: Okay? Is that better?

DR. LEITMAN: Illogical is good enough.

(Laughter.)

DR. LEITMAN: Yes, Ray?

DR. ROOS: I think that a lot of our decisions are based on risk benefits. And if somebody comes in the door and you determine that they are from the UK and you say, "You can't contribute to the pooled blood here," we only lose one donor, whereas if -- so the risk is relatively slight, whereas the recall of a large lot from 50,000 to 100,000 people, because of that one donor that's knocked through, there's an enormous burden that we pay for it.

So I don't really find it hypocritical. I think it's trying to sort out the whole risk benefit issue here.

CHAIRMAN BROWN: I agree. We're starting to vote, and we'll start with Larry. Hold on. All right. The question is: should FDA recommend new deferral criteria for donors of transfusable components, to attempt to reduce the theoretical risk of transmitting new variant CJD from transfusions

based on donor exposure to BSE in the UK?

DR. SCHONBERGER: Yes.

CHAIRMAN BROWN: Incidentally, just to remind the committee, it is possible to vote punt; that is to say, you can vote yes, no, or no vote -- abstain.

DR. HUESTON: Well, for my own benefit, I suppose, to walk through the logic -- and maybe for the benefit of Barbara because I think she raises a good point about how we proceed -- we have a situation with a small number of known cases of variant Creutzfeldt Jakob, all but one of which are in the UK.

However, we know there is a potential for widespread exposure to BSE that has already occurred. Therefore, we expect more cases, but we really don't have a good idea of the magnitude of the epidemic that we're going to expect.

Part number 2 says, "While there is no known whole blood or blood product transmission of classical CJD in humans, variant Creutzfeldt Jakob differs substantially from classical CJD." So we recognize that there is the potential for transmission of some of the transmissible spongiform encephalopathies via blood, albeit controversial

We have an animal model, and we can

identify infectivity in lymphoid tissues with variant Creutzfeldt Jakob, which is different from classical Creutzfeldt Jakob.

At the same time, it has been pointed out many times by a number of people that there have been no observed risk -- or no observed cases at this point of transfusion or blood product related variant Creutzfeldt Jakob cases in the UK. I think that's a little premature. One might say the absence of evidence is not evidence of absence.

At the same time, there are look-back studies in place in the UK, and there is a natural experiment -- a huge natural experiment ongoing in the United Kingdom, where if, in fact, there is a risk, I believe that the risk will first be apparent in the United Kingdom far before we would see it anywhere else.

At the same time, in looking at the precautionary principle --

CHAIRMAN BROWN: Is this the preamble for a vote?

DR. HUESTON: Yes, sir. You got it.

(Laughter.)

DR. HUESTON: If our goal is to be precautionary, but at the same time we have to

preclude having more negative impacts for any action that we take, then positive -- in other words, impacts on the blood supply. And I have struggled through the whole time, but I'm going to vote no at this time.

CHAIRMAN BROWN: Could I urge the remaining members of the committee --

(Laughter.)

CHAIRMAN BROWN: -- to vote rather than -- I appreciate it, and I let Will, you know, chatter on because he hasn't said a whole lot, and I wanted to hear what he had to say. And so thank you, but we'll never get through if we continue to explain the reasons for our votes, each one and all. So, Susan?

DR. LEITMAN: I take the opportunity to disagree with what you just said. I think the vote at this table is so critical, it will have such a huge impact potentially on the way America collects its blood, that if we go beyond our designated time it's worth it.

And I was influenced, and it was helpful to hear the last speaker's discussion. So I think if any of us have discussions or points to mention now, they might be valuable.

The deliberations of this committee are among the most difficult of any advisory committee