Donnelly's talk, which I entirely agree with her conclusions there.

We were asked to assess the magnitude of the risk that could result from the infective agent being present in blood. That's a pretty tall order, really, when we know very little about quite a lot of the factors that could affect that risk, particularly how many people may be incubating the disease.

Nevertheless, being good consultants, we said: Yes, we'll have a go at this and see what useful information can come out from that because we're not just looking at what the actual numbers might be but what actually are the lessons we can learn, what can we actually learn about the processes, particularly what can we learn about which components of blood and blood components are particularly risk factors. Are there particular groups of patients which may be more or less at risk? And can we say anything about the possible effectiveness of the different risk control measures which could be put in place?

Just to look at the time line of the study that we did, the study was initiated following recommendations from the SEAC Committee back at the end of 1997. There was an expert group meeting of a

fairly wide range of people in the United Kingdom fairly shortly thereafter.

Our study actually started early in 1998. We did a first draft report in April which then went to review by an expert, group of experts, in the external world, including both members of the United Kingdom SEAC Committee, some of the people around the table here today as well.

Then the final report was produced towards the end of 1998 after a fairly long gap, really, waiting for comments on the revised report. And the final report was then produced early this year.

It is useful to sort of look at that together with the times at which particular decisions were taken in the United Kingdom. In February '98 was when the Committee of Safety in Medicines made initial advice about imported plasma and then the decision, final decision, to implement leukodepletion of fresh blood supply was taken in July 1998, so very much in the process of the time we were working.

SEAC back here in 1997 had advised that the government should consider the use of leukodepletion. And there was a lot of work that was done immediately thereafter.

I think it is also worth just thinking a

little bit about some of the reasons for those decisions. Now, I wasn't part of that process, and there may well be others who were more closely involved. But if one actually looks at the press release which the Department of Health issued after that, this is Frank Dobson speaking in the press release, saying that he fully accepts the advice of the Committee of Safety in Medicines. He has decided that the bioproducts laboratory, which is our blood fractionation, plasma fractionation service, will be allowed to import plasma.

And then he says this will reduce the possibility of repeated recalls of blood products in the future and thereby help to maintain public confidence in these products.

So his initial reason was nothing about blood safety. It was about public recall of blood products. And that is reflected very much in the statement from the Committee of Safety in Medicines, from their minutes, where the first recommendation is that a plasma pool subsequently is identified as being strongly suspected of having new variant CJD should be withdrawn -- I'm paraphrasing slightly -- and then to avoid future withdrawals of large batches of medicine or products, including vaccines, manufacturers should

avoid the use of U.K. albumin as an excipient to medicinal products, so again concentrating as much, at least, on the risk of recall and the management issues that that arises as well as the health safety implications of variant CJD infectivity in blood.

Just very briefly -- I'm not going to go down these. These were a range of people whom we consulted during the process of the study, including people to do with the blood supply and blood fractionation service for the United Kingdom, people with the Haemophiliac Society in the United Kingdom, uses from haemophiliac centers, so a range of different people, both experts in variant CJD and people involved in the blood business in the United Kingdom.

And then the review panel involved a range of people, both from the United Kingdom SEAC Committee and others, who reviewed our report in detail, came back with comments, which were then taken into account in our final version. So the study has been fairly extensively reviewed and commented.

When we started tackling this, the basic presumption that we had was that variant CJD infections are caused in some way through exposure to the BSE infectivity through the food chain and that

will result in a number of cases.

What we needed to do was to then look at what that meant in terms of potential further variant CJD infections through the blood donation route, either through blood components or through plasma pools and plasma derivatives. How many patients were going to be exposed? And what is the potential for an effective unit coming in here, resulting in a new infection of variant CJD?

This is rather similar in a more diagrammatic form of the process which Christl put up, of the way in which you could actually try and model the estimate of infections there from the food supply.

In fact, when we started off, we presumed that in order to get certainly any absolute measure of the risk from the blood supply, we had to try and come up with some estimate of the size or the number of people who would actually be incubating variant CJD.

That was probably the big difference between the early draft of our report and the subsequent draft, when we looked at that issue in more detail and we realized that to try and come up with anything like a best estimate, even with significant ranges, was really not possible, that particularly we know little about the cattle-human species barrier.

We know quite a lot about these things pu here, as Christl said. We know the numbers of infected. We know the life expectancy of cattle.

So we know the numbers of advanced infections for the region, but, then, what does that mean in terms of the actual consumption of products and the number of cases which might develop?

So the two big unknowns in there are probably the species barrier between cattle and people and the incubation period for variant CJD when you're crossing a species barrier, in particular.

This slide I won't dwell on. It's, in fact, drawn from the Oxford group's data, again seeing that the peak of infectivity coming in is in 1989. And the bars on here are different ages before infection. Again, I think we're seeing that data already.

When we realized we couldn't come up with any prediction of the number of cases, we decided that the way we would present the risk would be risk of new infection per infected donor. What we tried to do in this slide is just to look at to get some indication of what the potential range might be, which, as we know already, is very large.

What we are seeing here is the fraction of

blood donations infected with variant CJD against time and plotted against the mean of the incubation period.

So we've got increasing incubation period up here. And if you see, at low incubation periods, we really have a very small fraction of donations infected: less than one in a million.

As we go out to larger incubation periods, say, if you look at 30, then we're getting up to a maximum of about one in 1,000. They can increase, and obviously they can increase beyond this, too, if one looks at other longer incubation periods. And that's just against one of the potential variable parameters that we have got.

I am just going to go very quickly over the evidence for infectivity in blood. I think probably that will have already been looked at significantly by this Committee, but it was very much part of the background for what we were doing in the study that we did.

If we look at blood transfusions, we know that all attempts to transmit infectivity of blood, blood transfusion, so across a species barrier, have failed and that within animal models, as far as I am aware, the one case which has been reported by Bob Rohwer is still the only case that I have heard of in

which there has been a positive transmission by the i/v route within an animal model.

Epidemiology studies have shown that's from sporadic CJD. There is no evidence that there has been any transmission through the blood route. And when we look at blood from human CJD cases, primarily sporadic CJD cases and certainly no variant CJD cases, and look at that, their infectivity through the i/c route into animal models, there have been a few experiments which have shown positive infectivity into rodents but negative results from a significant number of studies into primates and other species.

And there have been some questions asked about -- these cases, these experiments all involve very small numbers of animals and some sort of significant questions asked about those and, in particular, the fact that it is a bit odd that we have got no positive infections in the primates, which you might have expected would be more susceptible than the rodents.

Then when we look at actually within animal models themselves, there have been quite a number of cases, experiments where positive infections have been reported from animals infected with some form of TSE and have been through the i/c route

infected in the same species, so again with no species barrier.

So all that we can conclude from that is that the blood from an animal which has been artificially infected with the TSE could contain infectivity. And to some extent, that model may be the one that is most applicable to the situation of people being exposed to a TSE through food exposure.

Again, very briefly, a number of experiments that have been carried out trying to assess what the level of infectivity in whole blood is, ranging here from the low end of about five from some of Diringer's work to over 300 from Casaccia -- again, these are all i/c infective units per milliliter of blood -- and a value of about 10 from the work from Paul Brown and Bob Rohwer.

In deciding what we wanted to use as a base case for the work that we were doing, we decided that it was better to err at the low end. After all, these are all animal models which have been developed to enhance infectivity, enhance the likelihood of infectivity. So when we are looking at the human situation, we would be more likely to be at the low end.

We also have to take into account, as we

have already mentioned, that the i/v route, the peripheral route, is going to be less effective than the i/c route. We took a factor of ten for that, again one of the areas where you have got significant uncertainty.

So we took a value of ten i/c infective units per ml as a base case but with a range of values. And we looked at the uncertainty in that and with a factor of ten of the i/v route being less effective than i/c.

We then needed to know what was the level of infectivity in different blood components and in different plasma fractions. The only experiment which has been done which casts any light on that are the experiments which have been done by Paul Brown and Bob Rohwer. Again, I imagine you have already seen a lot of this data.

Two experiments: the spiking experiment, where you have got a high input of spiked hamster adapted scrapie, into human blood, which was then separated and fractionated and all the products of that titrated. I just want to note there, as I know the authors have done, that only a fraction of the infectivity was actually recovered in the final process and that the endogenous experiment, where

blood was collected from mice infected with a mouse adapted TSE, again separated and fractionated as before, and then inoculated back into experimental animals.

In the endogenous experiment, there was no transmission for some of the fractions, including whole blood and red cells, but the number of animals inoculated was fairly small. In fact, the expected number of infections for whole blood, for example, would have been less than one.

So what we did was to take the estimate of infectivity in whole blood. I'm now going to talk about intravenous infective units per milliliter. So we've got one i/v, i/v 50 per milliliter blood, so about 450 per conventional units of blood.

We have taken the relative infectivity in plasma and Buffy coat from the Brown and Rohwer experiment, from the endogenous experiment. And we have assumed that no infectivity is lost, so a significant assumption there.

If we do that, we can then get a breakdown of infectivity in the 3 components with about 50 percent of that infectivity being in the plasma, initially a surprising result possibly with the remaining infectivity being about equally divided

between red cells and Buffy coat.

Then looking at plasma derivatives, again taking that result for plasma, taking the result from the endogenous experiment, where we could use it for Fractions 1, 2, and 3 together, and cryoprecipitate, and then using the relative infectivity from the spiking experiment for Fractions 4 and 5, we can then get infectivity in the main plasma fractions.

We then wanted to go one step further and look at the infectivity in plasma derivatives, the actual products which were being given to patients.

I have been talking to a number of experts. We felt that there were two alternative ways of calculating that. One was to assume that the infectivity would partition in proportion to the protein content of the product. And the other was to use some kind of estimate of clearance factors from the various processing stages in a blood processing situation.

This slide shows the results of doing that, with the blue bars showing the protein mass content basis and the purple ones showing the estimate based on clearance factors. So this is infectivity assuming that plasma derivative was made 100 percent from infected units. So to get the actual level of

infectivity, you then have to multiply that by the proportion of units which were actually infected.

The red line here is unity. So if you're to the right-hand side of that, if you had 100 percent infected blood, then you would have one infected unit per average dose of each of these products. And if you're to the left of it, even with 100 percent of infected blood, you've got less than one infected unit per dose of product.

You can also see that there was wide variation between the two approaches, sometimes about six or seven orders of magnitude here for intravenous IgG, for example, with the protein mass content level giving a reasonably high estimate because you have got high dose about 90 grams, typical dosage for this product for certain patient groups but with a clearance factor basis having a relatively low estimate. So you have got significant variations here.

In the base case results we shall present in a moment, we used the protein mass content basis mainly because they were the more conservative. They gave the higher values. And we used the clearance factor approach as a comparison.

You can see that these two products, in

particular, for one type of factor, 8, this is the less pure version of Factor 8. Eight is not much different between the two.

You have got a potential infectivity greater than one. So if you've got high levels of a high proportion of donations infected, you could theoretically get infectivity through this route. And intravenous IgG is the other significant potential.

Here, particularly with this one, this difference is very significant because when we calculated the infectivity for the protein mass content, we took no effect of any subsequent clearance through the processing.

So we were just basing it on the initial infectivity and the protein mass content. And we assumed that subsequent processing steps would have no effect on the infectivity and the product, which is not very likely, I would guess.

What we then needed to do was to look at the way both the blood components and the products are used to actually get an estimate of the risk to the patients being exposed. The way we did that was to define a set of representative patient groups.

There were just not the data available that could have enabled us to look at the way the

products were actually used overall in the health service in the United Kingdom.

So, together with medical experts, we defined a set of about 20 different patient groups. We looked at the likely numbers of the patients in each group and the typical dosage to the range of different both blood components and plasma derivatives that they may be exposed to over a treatment period. So these are just some of the patient groups that we identified, and there is more data, obviously, in the report, which you have.

So we defined the treatment and the dose for each of these patient groups, both to blood components and to plasma products. And then by assuming a linear dose response model, we can then estimate the number of new variant CJD infections that could result from that.

And, then, the number of variant CJD cases obviously depends on both the incubation period. And, again, here you're not crossing a species barrier from cattle to people. You're within species. So the incubation period is likely to be less than from cattle to man.

You need to look at the remaining life expectancy of these patients and obviously their

probability of surviving the actual episode for which they are being treated.

I'm not going to concentrate on this because I don't think this is the important thing for this. This result shows the numbers of new infections per infected donation for some of the patient groups. So along the bottom here, we have the fraction of donations infected going from unity, on the right-hand side, to one in a million on the left-hand side.

We can see that for many of the patient groups, we're down here at less than ten percent of patients infected for a very wide range of fraction of donations infected.

For some groups, we are at significantly higher level than particularly the patients being given intravenous immunoglobulins, bone marrow failure given red cells and platelets, and acute blood loss being given significant numbers of red cells.

We see this fall off with the fraction of donations infected because with this group, we have a fairly small number of patients. And effectively we have infected all of them by the time we get up to this level. I think all we are saying in this is that there is a range of exposure for different patient groups but highly dependent on the assumptions that we

have made.

Overall we estimate that the number of new infections for the base case results are about 2.6 new infections, about equally split between the patients for blood components and the patients for plasma derivatives.

That translates into case of about 0.8. So we've got about 2.6 infections and about 0.8 cases because obviously not all of the patients infected survive long enough to become a case.

Obviously all of those results are highly dependent on the assumptions that we have made. And you can get some interesting insights into that by actually looking at the sensitivity to some of those assumptions.

So here is our base case for looking at new infections, about 0.8 new infections split between blood transfusion cases, plasma derivatives in red, and the green is increased because of patients, recipients continuing to donate.

If we reduce the infectivity by a factor of ten, we see that we make very little difference to the risk from blood transfusion, but we make quite a significant different to the risk from plasma derivatives.

If we reduce it by another factor of ten, we virtually eliminate the risk from plasma derivatives. But, again, the risk from blood transfusion cases stays about the same.

The reason for that is that in a blood transfusion case, you're transfusing typically a unit or more of blood. That unit contains, of the assumptions that we have more, more than 100 infective units of blood. So, even if you reduce it by a factor of 100, you've still got a significant risk of infection; whereas, the plasma derivative results are spread over a very wide number of people with a relatively lower level of exposure.

Conversely, if you increase the infectivity by a factor of ten, you then increase the risk from plasma derivatives very significantly, but, again, you don't do very much to the risk from blood transfusion.

If you look at the incubation period, the base case incubation period for blood supply we assumed was 15 years, so a 15-year incubation period for infection through blood supply. If you reduce that to five, you make a modest increase in the number of cases basically because more patients survive because you've still got the same number of infections

but more with a shorter incubation period, a higher proportion of them survive. And, conversely, with a longer incubation period, few of them survive.

So the basic conclusion, the first conclusion, which I think is perhaps important, is that it really is not possible to come up with any reliable estimate of what the real risk of variant CJD infectivity in blood is.

We don't know how many people may be infected, and fundamentally we don't know whether blood from someone with variant CJD could be infective. And we have no evidence to confirm that blood from a person with CJD would be infected. However, evidence with the animal model suggests that there is a potential risk, although we have not demonstrated that that is true yet.

Then looking at the results for the actual study, if there is infectivity in blood at the sort of levels that we have assumed based on the Brown and Rohwer work, then the infectivity that is present in a full unit of red cells would be sufficient to cause infection. That conclusion seems to be valid over really quite a wide range of different assumptions.

Plasma derivatives, the result is slightly different. If we look at the base case and our very

conservative assumption that assuming infectivity is based on protein content and taking no account of clearance factors, then there are a few plasma derivatives which could theoretically cause infection. But that conclusion is highly uncertain and varies very significantly over the assumptions that are made, and many of the assumptions tend to reduce the risk, rather than increase it.

So the overall message from that is that looking at risk from blood, it looks as if there's a high risk from the red cell units from the whole blood transfusions than there is from the plasma derivatives. That conclusion seemed to be fairly generally supported by the blood industry people in the United Kingdom.

In the U.K., we have looked at a number of risk reduction measures, including the initial recommendation from SEAC to look at leukodepletion of red cells on the basis that infectivity is perhaps more likely to be associated with white cells, -- that's perhaps a bit uncertain -- eliminate U.K. source plasma, and then a range of other possible measures, including reducing the use of blood obviously would help. Preventing transfusion recipients from giving blood, breaking the recycle

loop could be important and possible prophylactic treatment, although there's really no real data on that at the moment.

Just looking at the results of those, again, emphasizing very much looking from our base case, if we look at leukodepletion on that and assuming that the effectiveness of leukodepletion would be to reduce the infectivity by a factor of 100, then we actually see a modest reduction but, actually, a rather small reduction. That may be if leukodepletion is more effective than that or if the level of infectivity in the red cell unit in the first place was significantly less, then the effectiveness of leukodepletion would be significantly greater.

So if we looked at the range of possibilities, leukodepletion could be effective over quite a wide range of different possibilities, but it's not necessarily that effective.

Eliminating U.K. source plasma is obviously a pretty good measure assuming that the source of variant CJD is restricted to the United Kingdom and not from possible source countries, including the U.S. or primarily the U.S., obviously.

So that is very effective in reducing the risk from plasma products, but, as I said, the

likelihood is that this risk, the risk from plasma products, is overstated in the study. And it does very little, nothing, in fact, to the risk from blood components.

Reducing the use of blood obviously has an effect in proportion to the amount that you could reduce the usage of blood. There have been some interesting studies in the U.K. where you look at variations between different hospitals in their use of blood for the same operation, and there is huge variation, so obviously a scope there but a sensitive area, I suspect.

Restricting blood recipients from being donators obviously breaks the recycle loop but, again, has some potential implications on the blood supply.

So leukodepletion could have a significant benefit, but the potential effects are uncertain. Eliminating plasma, eliminating U.K. plasma, will eliminate any risk that there is, but the original level of risk might have been extremely small.

And a range of other measures has some possibilities. I think this one received quite a lot of attention in the U.K. recently looking at prophylactic treatment with Pentosan. There seems to be evidence that this could reduce susceptibility in

animal models, but there is an awful lot of work to be done I think before we could say with any confidence that that could work for variant CJD.

Thank you.

(Applause.)

CHAIRMAN BROWN: Thank you very much, Dr. Comer.

We have time for a couple of questions. I have a question. I know that a handful of patients who have died with new variant CJD have been identified actually as having donated blood at some point during their incubation period. I know that that ranges from a donation made as early as 1982 to donations that were made just within the past couple of years.

I think -- and this is where I need to be made accurate. I think some, if not all, of those donations were one-to-one blood transfusions or packed cells, but I'm not sure. Can you tell me, for example, if that is true or whether these donations found their way into plasma pools?

MR. COMER: I know for sure they found their way into plasma pools. I do not know the answer to whether they were whole blood donations or not. I think the answer to that is yes, but the policy that

they have taken in the U.K. is not to inform recipients, which is a difficult ethical debate, obviously. So I think there has been little publicity about that.

CHAIRMAN BROWN: Right. I know it is wrapped in considerations of confidentiality and patient privacy, but that will obviously be a crucial group to watch and may give you or us the first clue about the reality of whether blood is infectious from patients with new variant CJD.

Of the handful, I think one only or two of the recipients have been alive for more than five years, something like that. I think most of them are just a year or two.

MR. COMER: I think that is right.

CHAIRMAN BROWN: Yes. Questions? Bob?

DR. SCHONBERGER: Could you repeat the answer to the question that you just said? I wasn't sure. It's mostly plasma pools or mostly one to one?

MR. COMER: No. I know for sure that it's plasma pools. I do not know --

DR. SCHONBERGER: It's plasma pools?

MR. COMER: Yes. That is for sure because there were some recalls. I do not know how many were one-to-one blood recipients.

CHAIRMAN BROWN: Bob?

DR. ROHWER: Yes. I wanted to just comment that if I understand you correctly, you are doing your modeling based on the titers that were associated with the crude Cohn fractions in the paper that Paul and I published.

MR. COMER: Yes.

DR. ROHWER: In that regard, virtually none of those materials are used as is. They go through considerable additional refinement before they ever get into people.

We have in the interim completed several spiking-based validation studies, which have some caveats attached to them, of course. Nevertheless, the results have been uniformly very encouraging because we're seeing that in the process of carrying these fractions through scaled-down versions of the manufacturing process, we're seeing the elimination of very high levels of infectivity, suggesting that, at least at the level of plasma fractions, we have another very important additional level of safety that we're getting from the manufacturing process itself.

The other thing I wanted to ask you about was your modeling of the contribution from eliminating donations from persons who had received blood and

blood components previously.

I gather you are just looking at the next donation, you are not looking at the issue of propagation of the infection over time by that practice. Is that correct? Because you are showing very little effect here, and in terms of a safety measure, I have always ranked it as one of the most important things we could do.

MR. COMER: That is true. We didn't attempt to model that really fully. And it was just a very crude estimate over the first year. So yes, it is not a full representation of the effect of that.

Just going back to your first point as well, if we take the results from our estimates based on clearance factors, which I think there will be some differences in detail from the results that you have got now with your spiking experiments, if we base the risk from plasma derivatives on the clearance factor approach, then the risk from plasma derivatives is virtually zero. I mean, there really are very, very low levels of risk associated with that. So yes, you get significant, very significant, risk reduction.

CHAIRMAN BROWN: A couple of points just to bring your experimental data up to speed. Unpublished further experiments on the mouse model

have produced good news and bad news.

The bad news is that we have a disappointingly large number of transmissions following intravenous inoculation of either plasma or Buffy coat. We also have a transmission using whole blood as a transfusion into these mice. So that's not good news.

The other thing that is not too good is that we have now got in this particular model a ratio of five to one, as opposed to ten to one, which was also disappointing.

The only piece of good news in that in terms of experimental data is that we found that, again, in this model, the level of infectivity during the entire incubation period is almost negligible compared to the level of infectivity during the clinical phase of illness. And that is very good news indeed. So these are data that are not yet published but .--

MR. COMER: Can I just clarify that?

CHAIRMAN BROWN: Sure.

MR. COMER: It's five to one between i/v and --

CHAIRMAN BROWN: Yes, i/v and i/c. I mean, we were hoping for at least ten, but that's not

the way it happened. Again, there probably is variability from experiment to experiment. And the next time we do it, it might be 10 or 20 or 3. I don't know, but that's the initial number.

Other questions? Yes?

MR. COMER: Well, just commenting on your last point there about the infectivity through the incubation period, our assumption was that levels of infectivity are basically uniform throughout the incubation period, which is obviously the most conservative assumption you could make.

CHAIRMAN BROWN: Right, right. And, as I say, if it turns out to be the case with the human disease, -- and I'm guessing it probably will be -- with you, I think the likelihood of disease, natural disease, whether it be scrapie in sheep, BSE in cattle, or CJD in humans, is going to be quite a lot less virulent than the experimentally induced disease.

Even under the experimental conditions I mentioned, however, infectivity in all components of the blood during the incubation period is so low that it virtually poses I think no risk, at least in terms of plasma derivatives.

Other questions? Yes?

DR. HOLLINGER: Is it your assumption in

humans and, say, Dr. Donnelly's in cattle, that all infections lead to cases if followed long enough? That is, is there a chronic carrier assumed to be the case; particularly in cattle, that is? Do we know that at all?

MR. COMER: We assume that any animal infected will result in a case if it survives long enough. That is certainly the assumption I think both of us have made.

DR. HOLLINGER: Is there any data following for prolonged periods of time infected animals?

CHAIRMAN BROWN: There is if -- go ahead. I'm sorry.

DR. DONNELLY: Yes. I mean, I made the assumption, like Philip's group, that all animals that were infected would if followed for long enough lead to disease.

The possibility of carriers, we looked into the possibility of different susceptibility classes. Certainly I don't know of any study that has followed them long enough to be able to -- you tend to have them followed for up to seven years. I don't know of any studies that you do where they're followed for longer to look for these.

CHAIRMAN BROWN: The only study that I'm aware of that documents a carrier state is work in rodents in which mice were treated with Substance X. A few mice that were treated with -- it's the Pentosan-type drug I believe were shown -- maybe they weren't even shown to have infection. They died a natural life without developing clinical disease.

Bob, can you correct me or verify this? I'm not aware now that I think of it again of any study in which infection; for example, documentation by Western Blot or immunostaining of the resistant form of prp, where an animal has carried that all of his life and died from an abscess three years later, which would be the carrier state.

DR. ROHWER: Well, there is a recent report from Rocky Mountain Lab showing a situation just like that, where the animal survived its life span without showing disease, but it could be transmitted, then, subsequently.

There are also some very old papers from Alan Dickinson and his colleagues showing the same thing using certain strains of mice and also depending upon the route by which the animal is infected.

I would just like to caution in terms of thinking about preclinical infection, I think from my

perspective, anyway, route and dose could have a very big effect on exactly what we see in these models.

So to date, we have only really looked at the i/c model. I think it behooves us to look at more natural routes of infection before we draw any conclusions about the preclinical state.

DR. EWENSTEIN: I just wanted to make a comment about the use of the plasma derivatives. You have assumed 2,000 units as a single inoculum, I think. I just wanted to make the point that for most patients, there are periods of time when they might receive at least ten times that sort of dose in a matter of days.

Now, I don't know what the cumulative effect is over the space of a couple of days. Over the course of a year, a typical number might be 80,000 units. Again, we don't know the cumulative dose because we don't know the body's ability to clear whatever the infectious agents are.

At least in clinical practice, there would probably be many instances where there would be at least 10 times that exposure in a matter of 48 or 72 hours.

MR. COMER: Yes, obviously what we've done here in looking at the typical -- you know, defining

the patient groups and the exposure is just to give some estimates against which we can base some calculations. And there are a whole range of different variabilities that we could look at.

When we actually looked at the effect of changing some of those assumptions, their effect on the results were mainly fairly marginal. So you wouldn't get a big difference by making that sort of a change.

CHAIRMAN BROWN: We have time for two more questions.

Yes, Dr. Leitman.

DR. LEITMAN: This is for Dr. Donnelly. One of the most compelling pieces of data that there's blood transmission of the agent is through the maternal to fetal transmission in cattle, and you quoted a risk of 10 percent over the last six months of gestation.

That's all from clinically observed information? There's no experimental data on that? That's question number one.

And question number two: Couldn't that not also be due to an increased genetic susceptibility to infection in the same -- passed on from the mother to the calf?

DR. DONNELLY: Well, we looked at two main sources of data in looking at maternal transmission. There was the maternal cohort study which was organized by Ministry of Agriculture staff. And unfortunately, rather than recruiting calves just as they were born, they were actually recruited after they had been in farms for a period of time.

There was a maternally exposed animal and a control animal. About 300 of them were recruited. But unfortunately, those animals both in the maternally exposed and control would have been potentially exposed to infectious feed while they were on the farm.

Now, from that experiment alone, it is quite difficult to distinguish whether or not it's maternal transmission or whether or not it's genetic predisposition. And that's because all the experiment -- or all of the maternally exposed animals were recruited as the last calf, so you didn't have a long period of time, a spectrum over the maternal incubation period.

But, looking at the main database, which has been collected on all BSE confirmed cases in Great Britain, we were able to look at those for whom the mothers had been identified and look at dam calf pairs

of BSE cases.

And if you do that, taking into account survival of both dam and calf, you're able to see an increased risk for those animals born at the end of the maternal incubation period, but no increased risk for those born two or three years prior to onset.

So that definitely suggests that it is maternal transmission rather than a genetic predisposition. And that, I suppose, is something to note as well in the potential for carrier animals is that genetic studies that have been done have -- with one exception, which was not followed up with additional experiments, have generally not shown a genetic link in cattle and predisposition.

CHAIRMAN BROWN: Is this directed to -- yeah, okay.

DR. PRUSINER: I would just like to ask you one question. What do you think the mechanism is for a cow near the end of its incubation time so it now has high titers in its brain and it's more likely to infect a calf that's born to it than earlier on?

That's what you're saying, correct?

DR. DONNELLY: Yes.

DR. PRUSINER: That's the strongest data you have. The first piece of data that you -- I don't

mean to be tough about this, but I think the first piece of data you quote, the cohort study, tells us nothing.

It's zero because of the way the animals were ascertained, they way they were taken into the study. So I think to quote the study constantly is really a mistake. It doesn't -- it's not a clear study. And I think that people in Britain are equally divided amongst what this study means.

So the second study is the one you're quoting now. It's your study. And I don't understand the mechanism.

DR. DONNELLY: I don't understand the mechanism either. I mean, what we were looking at was increased risk as it was associated with incubation stage. And as an epidemiologist and statistician, I don't think we'll ever get at the mechanism in that manner.

One thing that was interesting was an examination of beef suckler calves that John Wilesmith looked at, was to try and look to see what the transmission rate is there. And it was kind of a smallish sample size, but it didn't show any increased risk in those animals that had suckled for approximately a year.

So that suggests it probably wasn't milk because, had it been milk, you would have seen a differential in risk. But otherwise, I don't think that all the statistics in the world and the biggest sample size we'd ever actually be able to tell the mechanism.

CHAIRMAN BROWN: Yes, Linda.

DR. DETWILER: Looking at the database and looking at the calf sample, did you look over the entire course of the epidemic or was it concentrated to a certain point of time with the calves?

Because that might -- exposure to feed, too, during their life span might play a difference in the --

DR. DONNELLY: The data was mainly on BABs, or born after the ban, cases. But we did control for what the risk from feed would have been in their herd. So there was a control for what they probably would have gotten to see the expected number of pairs we would have seen.

So we look at the number of cows and the number of offspring that were cases and how many -- within that herd, how many pairs you would expect. So it is controlled for what you'd expect their feed risk was.

DR. DETWILER: What year specifically, do you have that?

DR. DONNELLY: Oh, born after the ban calves, those would have been -- they were mainly born in the second half of '88, '89 and some in '90.

CHAIRMAN BROWN: Mike, sorry to keep you standing so long. You have a comment?

DR. BUSCH: Thank you. Yeah, just a comment/question.

The hemophilic community often frame themselves as the canaries in the mine, and I think here obviously the British population are the canaries vis-à-vis transfusion transmission potential. We're ten years out from the peak of the BSE epidemic, and I'm just curious, from your models, at what point in time downstream would you begin to conclude that transfusion transmission is not an issue?

As this committee begins to deliberate, I think it's important to consider any ban that might be implemented on U.S. travel to Britain. How long will that be in place, and can the experience in Britain give us some sense of when we could discontinue such a ban were one introduced?

MR. COMER: I don't think we can really answer that at all because we still know very little

about the incubation periods both from cattle into man, so when might the peak of variant CJD cases be in the United Kingdom, and also what the incubation period within the blood supply would be.

We simply don't know the answer to either of those questions. And I think we'll be a number of years yet before we can really use the data to give us a better feel for what those numbers are likely to be. So it's not going to be short.

CHAIRMAN BROWN: Larry, the last comment now.

DR. SCHONBERGER: This would be for Donnelly as well. My understanding is that the oldest new variant case of CJD is in the early '50s. You mentioned that you had data that cattle at different ages had a different susceptibility to BSE.

And I was wondering how strong that data is. You talked about an increase susceptibility between the ages of six months and 18 months, but that the exposures, you implied, were as great under six months and over 18 months as during that period, and yet your statistics didn't show that the cattle were coming down.

Is that what you were trying to say ?

DR. DONNELLY: Well, through the

statistics alone of the back calculation, you can only get what's the convolution or the combination of exposure to susceptibility together. But it's by additional data from looking at farmers and what they say they do in practice that exposure seems to be within one order of magnitude about the same all the way through.

But you do seem to have this window.

DR. SCHONBERGER: You mean after 18 months --

DR. DONNELLY: Yes.

DR. SCHONBERGER: -- exposure was just as great, but your --

DR. DONNELLY: Yes.

DR. SCHONBERGER: -- data does not show that they're coming down with the disease?

DR. DONNELLY: Oh, yes; and if anything, it gets greater at 24 months when the cattle start milking. One thing I didn't have time to get into was the fact in doing our analysis of the variant CJD epidemic, in addition to requiring consistency with the annual incidence of cases, we also require consistency with the age distribution of cases.

And in doing that, we're only able to reproduce the age distribution of the cases observed

today if there is some age dependency. That can take the form of an age dependency in the incubation period distribution, or it can take an age dependency in exposure susceptibility.

Now, it's difficult to imagine what the biological mechanism, even if you could work it out in cattle, would necessary apply to humans. But also with humans, you have considerable difficulty of hard to quantify differences in characteristics of dietary choices with age.

But there does appear to be something. We don't yet know what it is. But through time, in the next couple of years, we will hopefully be able to get more data to tell whether or not we can distinguish between it being an age dependent incubation period and age dependent exposure susceptibility.

But in the cattle, it's very clear: you can't get a fit to the data just on the basis of constant susceptibility, or even susceptibility peaking at birth and dropping right off.

CHAIRMAN BROWN: Thank you very much, both Drs. Donnelly and Comer.

It's now high noon. And I had been reading the agenda from a draft and inadvertently left out a presentation by Dr. Stephen Nightingale about

the meeting held by the Advisory Committee on Blood Safety and Availability about the reserve capacity of U.S. blood supply.

He will speak next, and he will be followed by Dr. Penny Chan. Both speakers have kindly agreed to limit their presentations to 20 minutes so that we can remain on schedule.

Dr. Nightingale.

DR. NIGHTINGALE: And if possible, less.

Dr. Brown, members of the committee, and ladies and gentlemen, what I will try to do, and do in the next ten minutes, is to summarize the meeting of the Advisory Committee on Blood Safety and Availability that was held on April 29th and 30th of this year to examine the reserve capacity of the United States' blood supply and to recommend how it might be strengthened.

But before I change that slide, since Dr. Freas and Dr. Brown raised the issue, let me briefly, within 30 seconds, go over the jurisdiction of the Advisory Committee on Blood Safety.

It was chartered on October 9th to advise the Secretary and the Assistant Secretary on a broad range of issues which include: implications for blood safety and availability of various economic factors

affecting product cost and supply; definition of public health parameters around safety and availability of the blood supply; and finally, broad public health ethical and legal issues related to blood safety.

So I would say, Dr. Brown, yours is, by no means, the only committee which has jurisdiction with which ours overlaps. I am sensitive to the concerns that you raised in your earlier comments and will take them to the Surgeon General.

The committee -- could I have the next slide, please?

Dr. Satcher opened the April 29th meeting of the Advisory Committee by noting what is on the slide here, "that it may be necessary, at some time in the future, to defer, at least temporarily, some portion of the donor pool in order to maintain the integrity of the blood supply."

Dr. Satcher emphasized the need that this be done in a way that would minimize the impact of this action on those who depend on blood transfusions for the health and even their lives. He charged the Advisory Committee to review the state of the reserve capacity of the United States' blood supply and to recommend how it might be strengthened.

He further charged the Advisory Committee to do so before, and not after, circumstances might require use of this reserve capacity. And he concluded his charge by reminding the Advisory Committee that we should never be in a position, as some have suggested we may have been in the past, where we would feel obligated to release a unit of blood if we had any doubt whatever about its safety.

Could I have the next slide, please?

After introductory comments about the current safety profile of the blood supply, Ms. Marian Sullivan of the National Blood Data Resource Center, which is an affiliate of the American Association of Blood Banks, then described the current availability of the blood supply on the basis of data available to her.

She stated that, in 1997, about 12.6 million units of blood were collected and about 11½ million units of red cells were transfused; 93 percent of allogenic units were transfused; 2 percent were discarded because of screening test results; 4 percent became outdated; and 1 percent were unaccounted for.

However, as shown on this slide here -- leave that right where it is. Turn that slide back on, please. Okay, shown on this slide, total blood

collections have decreased by 5.5 percent between 1994 and '97, while the total number of whole blood and red cell transfusions increased by 3.7 percent during the same time.

And extrapolating from the current trends and making the assumption that Ms. Sullivan reiterated several times, the available blood supply in the year 2000 would be 11.7 million units of red cells, and total demand would be 11.9 million units.

There were three substantive comments made during the discussion that followed this presentation. The first was that most outdated units are Group AB blood donations which can only be transfused, I think everybody in the room knows, into a Group AB recipient.

The second comment was the fact that while the overall supply of blood exceeded overall demand during 1997, that did not mean that there were not local shortages during the year. And indeed, there were.

The final comment was that one factor contributing to the trend that Ms. Sullivan described is the aging of the population. About half of all transfusion recipients are over 65. As a result, as the population ages, there will be proportionately

fewer donors and proportionately more recipients.

After that -- you can just leave that there for a while -- Dr. George Schreiber of Westat ~~and~~ National Heart, Lung and Blood Institute sponsored retroviral epidemiology donor study, then discussed how donor retention might influence the reserve capacity of the blood supply.

He began by noting that, while almost half of the adult population of the United States has donated at some time, only about 5 percent donate during a given year. In 1995, about 32 percent of roughly eight million blood donors were first time donors.

Half of these donors never returned, and two thirds of those that did returned during the first year after their initial donation. Dr. Schreiber estimated that if the rate at which first time donors returned for a second donation within one year could be increased by 15 percent, the blood supply could be increased by 10 percent.

The discussion that followed focused on the suitability of these donors that might be induced to return. Dr. Schreiber has found that individuals who had donated only twice had no greater incidence of HIV or hepatitis C than individuals who had donated

more than twice.

A similar observation has been made about paid plasma donors. Paid plasma donors who return only once, regardless of the interval after their initial donation, appeared just as suitable as those who returned more often and/or more frequently.

After that, Dr. Alan Williams of the American Red Cross Holland Laboratories discussed some preliminary data on the use and effectiveness of incentives to increase blood donation. Again, Dr. Williams emphasized that his data was preliminary, and I will emphasize that again for him.

What he did report was he found that the number of donors who report receiving some non-token compensation had increased from 26 percent in 1995 to 62 percent in 1998. And in a survey of blood donors, Dr. Williams found that future blood credit is the incentive that would most strongly encourage them to give blood.

However, donors indicated that lottery tickets might actually discourage them from making future donations, and that cash incentives might tempt some donors not to disclose a deferrable risk.

Dr. Busch then spoke of the Blood Centers of the Pacific, and he discussed differences of risk

factors among blood donors. Dr. Busch, I think, will be speaking this afternoon in the public comment period, and Dr. Busch will speak on his own behalf on that point.

However, I would note that Dr. Busch's presentation was consistent with the observation of Dr. Schreiber and the plasma industry that single repeat donors are as suitable as multiple repeat donors. And Dr. Busch's presentation supported the suggestion of Dr. Schreiber that we focus efforts to expand the reserve capacity of the blood supply on efforts to increase retention of first time donors.

Dr. Gilcher, who is also in the audience and on the committee, did discuss new technologies that might increase yield per donation. He said, however, that because of the increased cost, the increased interval between donations, that this was unlikely to be a significant -- provide a significant addition to the blood supply.

Now, in the public comment and the Advisory Committee discussion that followed, the consensus emerged that retention of more first time donors, as Dr. Schreiber suggested, was the strategy most likely to increase the capacity of the United States blood supply and least likely to increase its

risk.

There was also consensus that it would cost a substantial amount of money and incentives, direct or indirect, to retain these first time donors, and that blood banks could not fund these additional costs from current revenues.

However, no consensus was reached on what, if any, incentives, up to and including paid donations, would be effective, how much they would cost, or who would pay for them.

With that in mind, the Advisory Committee then addressed the issues of what, if anything, individuals with hemochromatosis or the blood substitute industry could contribute to the reserve capacity of the blood supply.

There was substantial discussion on that issue in the long run. The most substantive discussion was by Dr. Al Grindon, who presented a range of estimates of the potential contributions of therapeutic phlebotomies from individuals with hemochromatosis.

These estimates range from 300,000 units per year, or 2.5 percent, of the current blood supply to three million units, or 25 percent, of the blood supply. Dr. Grindon's own estimate was on the lower

side.

After further discussion, the Advisory Committee did unanimously approve a motion that since blood products obtained from persons with hemochromatosis carry no known increased risk to recipients attributable to hemochromatosis, per se, they may be a valuable resource to augment the diminishing supply.

The Advisory Committee recognized the obligate need for phlebotomy can constitute undue incentive for blood donations due primarily to financial considerations. For this reason, the Department of Health and Human Services, they recommended, should create policies that eliminate incentives to seek donation for purposes of phlebotomy, and that, as such undue incentives are removed, the Department should create policies that eliminate barriers to using this resource.

Finally, the Advisory Committee heard presentations from representatives of the blood substitute industry on the potential contribution of blood substitutes to the reserve capacity of the blood supply.

The consensus of these presentations was that proof of principle had been established for these

agents, but unequivocal demonstration of safety and efficacy in adequately powered Phase III clinical trials had not yet been accomplished.

For this reason, it appeared to the committee unlikely that any of these agents would be able to make a meaningful contribution to the reserve capacity of the blood supply within the next two years, but quite possibly they could do so at a later time.

Let me have my last slide, which is a summary of the recommendations that the -- the summary is that demand for blood is increasing at about 1 percent per year and supply is decreasing at about the same rate. The extrapolation from the current trend says demand is expected to exceed supply in the year 2000.

The strategy that appears most likely to increase the reserve capacity of the blood supply -- and again, least likely to increase the risk of blood transfusion -- is to increase retention of first time blood donors.

However -- and these are important. However, there is no guarantee that this goal could be achieved. No firm estimate of how much it would cost and no certainty who would pay for it.

And finally, the complementary strategy to increase the reserve capacity of blood supply is to eliminate undue financial incentives for blood donations by individuals with hemochromatosis. And as such undue incentives are removed, to create policies that eliminate barriers to this use.

However, the potential contribution of this resource, while it may be substantial, is again there is no guarantee that this potential will be realized.

(Applause.)

CHAIRMAN BROWN: Thank you very much, Dr. Nightingale, for a lucid and concise presentation of the Advisory Committee's deliberations and conclusions.

Unless there are questions for Dr. Nightingale, we will proceed then directly to Dr. Penny Chan, who will report on the Canadian viewpoint which, as I understand it, is in flux with two meetings bracketing this one as though the Canadians want to see what we're going to do before they make up their mind.

DR. CHAN: Well, what can I say? I promise I won't speak as fast as Dr. Nightingale. Probably not as clearly.

I'd like to thank you first. And I probably -- although this was the meeting that I was asked to speak about held by the National Blood Safety Council on variants of CJD and issues for the blood system, I think I need to talk a little bit about our process and the background that brought us to these meetings before I go into a description of the meeting.

So, if I could have -- what I'd like to talk about is a little bit about what the council is, what the issue was, the process, and the background around which this meeting was set.

I'll go through just the agenda, very briefly mention a few things about the actual meeting, then the recommendations, and, although the meeting was held less than a month ago, what has happened since then.

So very briefly, the National Blood Safety Council is probably the Canadian equivalent to the Advisory Committee on Blood Safety and Availability that Dr. Nightingale was talking about. There are a few differences, some of which I may highlight.

It has 16 members. Three are consumers. Two are from industry. I should stress that none of the members are representatives of an organization.

They were invited for their experience and their expertise, but not as representatives.

And when I say industry, both the members that come from industry come because of fractionation, experience and perspective. And we don't actually have any people from the current operators of the blood system -- that is, the collection blood services.

However, within the group that I've listed under treating physicians, we have an ethicist, we have a hemophilia treater, we have several people with the experience in apheresis. We also have a couple that have been involved in the blood services previously.

We've got a couple of people, public health officials. And this is significant not only because of their expertise, but because of the regional and more local basis for public health. So it gives us sort of a broader dimension to the discussions.

We've got a hospital laboratory technologist, a lawyer and an anesthetist. Our mandate is to advise the federal Minister of Health directly. We are -- independent staff, I guess, is me, which means that I don't work actually for the

federal government.

I'm not within the actual Department of Health. My job is to support the council entirely, so that is a slight difference. And this, I'll get into a little later, means that the council determines its own agenda, the issues that it will deal with.

The history, just very, very briefly. I'm sure you're all fully aware of the Commission of Inquiry that took about four years and focused a tremendous amount of attention on blood safety, on decision making, and, as I'll describe a little bit later, set the background very strongly.

At that time that the report was released, the Minister of Health announced the formation of this council. And it was seen as a means of overseeing blood safety, of helping to prevent such disasters occurring, opening a dialogue, etc.

He named initially just seven members. And there has been a period of probably a year where we've expanded the membership, determined the mandate and all of that.

So, the functions have sort of been broken down into three. These are the functions of the council. One is more or less a watchdog over the blood system.

Now, as we advise the federal minister, it's largely the structural organization and performance of the federal departments, which are the regulator equivalent to your FDA, and the LCDC, which is equivalent to your CDC.

So we have a mandate to watch the actions, the organizational structure, is this the best for maintaining the safety of the blood system. We also have the role of helping to identify any risks to blood safety that the council may consider are not being dealt with.

And we have a very strong role in communication, and this means putting the parties together, having consumers being totally open to the public in information exchange, education, and certainly provide a forum for open debate on any issues.

We have two types of meetings. There are planning meetings which, as I mentioned before, we set out own agenda. It is not set by the government, therefore it takes a time to work out how and what the issues are. And we do have fairly frequent meetings with the Minister of Health.

And then we have open forums. And it's going to be the third of the open forums that I'm

going to be describing. The outcomes are not necessary that we have to come out with recommendations. We're not given questions to answer.

If we think there's a recommendation that needs being made, then council will make it. If the process has been sufficient, the people have got there and talked about things and courses of action become fairly obvious, then hopefully we can facilitate that process.

So the issue that we dealt with in early May was "do variants of CJD pose a risk to blood safety?" And we sort of divided it into the classic variant and others. The others came out of, I'm sure you're all aware, of the scare that we all had over the Utah donor was this a possible chronic wasting disease, etc.

So we just put that issue on the table and let's see where it went. Our process -- we circulated a notice widely to all associations, consumer groups. We've sort of got a mailing list that's growing.

The day before the meeting, there was a flurry of activity. The two blood service organizations in Canada both issued a press release. And I think it was either that day or the day before the regulator had also issued a letter to the blood

services regarding donor deferral and variant CJD.

So I have to tell you that obviously it wasn't council that put this issue on the table. There was a tremendous background that we set our meeting on. And I did already mention the climate that has been set from the Krever report and some significant impact on the way we're dealing with things.

The first, and probably most significant, is there's been a total reorganization of the blood system such that the Red Cross is no longer running the services. We now have two blood service organizations. Héma Québec is in the providence of Québec, and Canadian Blood Services over the other provinces and territories.

And there were some principles -- I've called them principles. You can talk about them as standards, but sort of moral standards that came out very strongly out of the report. And I think there's very heightened awareness of these issues still in Canada.

And these I've labeled the precautionary principle or perhaps safety is paramount. And there were two things that Justice Krever laid out fairly clearly that you should not await scientific certainty

to act, and you should also consider the likelihood and the severity when you're considering risk.

And I'll go into a couple of quotes from the report because I think they're fairly important for a background here. He also talked about "the importance of national standards, but that they should be local variation if it was deemed important for protecting safety and independent decision making."

So that's sort of the general background or environment. And then specifically, on the area of new variant CJD and the possibility of deferring donors who had resided in Britain, at the end of 1998, there was a report released by the Bayer Advisory Council on bioethics in Canada.

And it had 20-odd recommendations, one of which was that donors who had resided in a BSE country should be deferred from donation. And then, subsequently, I think it was in January of this year the LCDC had asked for a risk assessment to be performed on new variant, and that report contained a recommendation also for the deferral of donors from UK.

And then we do have what is called the Expert Advisory Committee on Blood Regulation, which, like your plethora of committees, is equivalent to

your BPAC. It's a more technical advisory committee to the regulator.

Their meetings are not open to the public. And they had also considered this issue and made a recommendation to the regulator on the issue of donor deferral. However, they had asked to await the data on -- now, if you want to know whether that's a spelling mistake, yes, it is, but it could be considered as a -- the implications or the impact so that you have a new word for it -- that's the donor survey.

Now, I've just copied a few -- and I've really cherry picked excerpts from Krever Report, those that were discussed in the meeting that set a sort of a standard here.

And the first excerpt I've chosen was "the operator of the blood supply system and the health protection branch must not wait for scientific certainty about the spread of a transfusion or infusion associated disease and the effectiveness of particular risk reduction measures before they actually reduce risks."

Now, that second part means that just because you cannot totally eradicate the risk doesn't mean that you shouldn't consider taking actions to

reduce the risk if there are actions that are possible.

And the balancing of risks and benefits of taking action should be dependent not only on the likelihood of the risk materializing, but also the severity of the effect if the risk does materialize on the number of persons who should be affected and the ease of implementing protective or preventive measures.

And clearly, the more severe the potential effect, the lower the threshold should be for taking action. So you can see we're setting standards here.

It recommended that Canada "have a national system for the collection and delivery of blood components and blood products." That clearly was not implemented. We have two systems.

However, a national blood supply system will have national standards to ensure that all persons in Canada needing blood components or blood products have access to products of uniform quality.

Now, this poses a little bit of an interesting dilemma. And even within the report, like most things that some people refer to as the Bible there, you can find a quote that says something that's a little bit different.

And so another excerpt says that "the National Office of the Operator must create an enforced national standards, but it should permit its local centers to exceed them."

So, as long as you've got a minimal standard, then regions can take actions or should take actions to exceed those standards if it's necessary.

It's recommended that the "Bureau of Biologics and Radiopharmaceuticals" -- that's our regulator -- "make decisions with respect to the safety of blood components and blood products independently of those made by manufacturers and distributors."

Now this one has a lot of historic significance, and perhaps I've only used it here to say that really the manufacturers and the regulator need to make independent decisions: "Obviously the manufacturers have to meet the regulatory standards; however, they can exceed them."

And that's what the next part is, that "the regulator accept manufacturers' or distributors' decisions to take actions that exceed the standards of safety set by the Bureau." And I think this is the final quote.

"The regulator should never interfere with

the decisions of a manufacturer or the operator to take a risk reduction measure that exceeds its regulatory standards."

I realize that I've spent rather a lot of time on that, and I apologize. But I think the context for the meeting is fairly important. I very briefly, on the next two, outlined the agenda. I've taken off some of the details.

And, as you will notice, your Chair here today was also the person who started our meeting off, and I might say he started it off by saying two things. One is, "I intend to be controversial." And secondly, he also said, "If you're looking for answers, you're not going to get them."

So that having been said about our meeting, the first section was really the overview. It was an information session, but we also tried to capture the experimental data that was available. And following strictly the experimental data, we went into a panel discussion where we asked what's the likelihood of transmission by blood and blood products.

Unfortunately, in the discussion, the distinction was not kept perhaps as clearly as it should have been between the components and the

products. And is it likely to be the same for classic and new variant?

And thirdly, the question was: What is the biological plausibility, from our experimental data, that there will be other variants of CJD? I won't go into the attempts of answering these.

We had a discussion by Dr. Will about the situation in the United Kingdom with respect to new variant and the actions they had taken. We had descriptions of what's going on in Canada, particularly on the surveillance system that we have for CJD in Canada; the current prion research; the precautions; and, for blood safety, our regulatory policy and our policy development.

Then we had time for submissions and discussion, and a panel discussion again.

If we can go to the next slide.

The second day we figured that we would change gears because we were not just looking at the science, but we were looking at the area that Dr. Brown had said: When we don't have the answers from the science, but we still have to develop policies, what are the things we need to consider?

And Dr. Hoots, who is also a member of the Blood Safety and Availability Committee here in the

U.S., did kind of a nice overview of some of the factors that are important.

And Mr. David Page, who is a hemophiliac, and he talked about some of the factors that are very important in the decision making from the perspective of consumers. And one of the critical things, and perhaps why I've gone into the Krever setting the standards, is the tremendous loss of faith in the blood system and the implications for scientists, physicians and people who have to make decisions and why this has to be a factor to be considered when you are making decisions. Then we had the recommendations that I've already described, one from the Bayer Bioethics Report, and one from the Risk Assessment Report that was given to the LCDC. And then we had the impact of deferring donors.

And Dr. Marc Germain and Dr. JoAnne Chiavetta presented the data from surveys that were not unlike those that Dr. Williams just presented. In fact, I believe there was collaboration in the establishment of the types of questions that were asked.

I'm not going into the data here. Dr. Germain and Dr. Chiavetta are both here and any questions about that should really be addressed to

them. I will make just two points. One is that the data vary between the two organizations and, like Dr. Williams said, within regions for each of the organizations, particularly for the Canadian Blood Services.

And perhaps the Canadian Blood Services data are more analogous to those of the -- the one that was conducted here in U.S. I really won't say anymore about that. As I say, the raw data, I think hopefully, will be circulated to you all.

Then we had submissions and discussion on the impact. And the last part of the second day we devoted to look back notification of recipients. And we had a description of a process that had gone on that started from the actual notification, the follow up after the notification, and, I might say, the lawsuits that are still pending over it.

We debated some of the ethical issues, and then we had a very interesting consumer panel which consisted of people who -- we had David Page, who is a hemophiliac, from his perspective. We had a thalassemic who is a constant user of components.

And we had a couple of parents of children who had been notified that their children had received products that were CJD implicated when that was the

policy in Canada.

So that was our meeting. And then I think I would just -- oh, yeah, there you go. That's the data from the survey. It will be circulated, I promise, and we can discuss those.

Finally, the recommendations that council came up with. And the first is a little long winded, but what it's trying to say here is, consistent with the letter from the regulator that went out, as I said, the day before the meeting, that members of Héma Québec and the Canadian Blood Services should get together, and we were prepared to serve as the independent third party, to make decisions about deferral of donors who have resided in the UK such that there is a single, high standard.

Donor deferral policies must be coupled with strategies to increase donor recruitment. So that's really not giving a time, but saying that the two organizations have to work out a single standard and that council would facilitate that process.

The rest of the recommendations I'll go through very briefly. Health Canada had not standardized its -- not finalized its policy on classic CJD, and we advised that they do so.

The blood services should provide clear

statements about the reasons for believing that there are no longer concerns regarding the classic sporadic CJD; that Health Canada and the blood services provide communication regarding all aspects of product quarantine.

And that was because there's considerable confusion over the Utah donor case. Health Canada identify and provide information that all products that contain trace amounts of blood products -- this was interesting.

Many of the physicians did not even know which products that were being distributed contained blood products. We thought this was an important issue. All products can be tracked in the event of an infected donor. And that they take steps to discourage manufacturers from using blood products in the production or formulation of other products.

That mechanisms are developed to ensure that -- oh, this is the surveillance for CJD. That criteria have to be established to determine between classic and variant forms, which I know is the topic that you are going to be discussing this afternoon.

And that these criteria should be very clearly put out to people and it's clear what they do when they get a case.

There was concern about the partitioning of the experimental data regarding the partitioning of the prion with the cryoprecipitate. And this recommendation says that the use of cryoprecipitate should be reviewed.

Finally, I think -- I keep saying finally. I think I'm getting to the end. That the information -- oh, that our equivalent to the BPAC, their recommendations be made more public so that people know when these things are going to occur; that Health Canada take the steps to ensure that notification policies are consistent.

And this was felt very strongly, the next one, from the consumers because notification without education and follow up is worse than no notification at all. All notification programs must include appropriate education and follow up components.

That Health Canada then ensure that the recipients notified in the past are informed of the facts and the policy changes. And that Health Canada ensure the simple, clear education of the public and physicians on CJD as it relates to blood transfusion.

Since May 7, 1999, lots of things have happened. However, the decisions have not been made. There is a deadline of June 10th which the regulator

has asked the operators to decide how long and what deferral criteria will be put in place.

And there are several meetings. The CBS has convened yesterday, I think it was, a meeting of their advisory committee to help them look at all the implications of donor deferral.

And the meeting that's scheduled to have the operators together to make a decision will occur, we hope, next week. There have been lots of other things. But I hope that gives you a little bit of an understanding of our process and perhaps the environment in which we're dealing with many of the same issues that you are.

(Applause.)

CHAIRMAN BROWN: Thank you very much, Dr. Chan.

Do we have a question for Dr. Chan? We could probably work any comparative discussion into this afternoon's open public hearing or committee discussion.

Yes, Jay.

DR. EPSTEIN: The issue of elasticity of the blood supply arises any time you contemplate deferring donors. And, you know, there was loose talk about UK exposure related deferral reckoned by, you

know, even just weeks to months of exposure.

And I just wonder, is there any figure that you can provide that represents what you think the Canadians believe can be recovered by new recruitment or increased frequency of donation?

In other words, what percent donor loss through deferral do you think your system tolerates?

DR. CHAN: I will not -- I cannot answer that question, but I can say that the types of -- the two services will have quite different elasticity. There's absolutely no doubt about that. For one, the inventory levels are different between the two organizations, plus the number of donors that would have to be deferred if you drew the line at one month or six months.

These are two numbers that have been bandied around, but I really would much prefer either or both of the operators to speak to that if you want a specific answer. Different is the issue. Maybe 5 percent was the number that was bandied around.

Is that sufficient, or can we -- okay.

CHAIRMAN BROWN: Larry.

DR. SCHONBERGER: When we had the problem with the human growth hormone, the solution turned out to be to switch to molecularly engineered hormone. Is

there any such solution to our blood problem in the near future?

Does anybody have any information on that; that is, using some substitute that would not require the human donator?

CHAIRMAN BROWN: Well, Factor VIII is available as a recombinant. I don't know of any other derivatives are yet available.

DR. EWENSTEIN: Let me comment on that. I mean, you're right, Factor VIII is available. There's still albumin in many of the preparations, although there are movements afoot to slowly release products that don't have any albumin as stabilizers.

There is a Factor IX product that's available without any human component. But there's still a group of patients even in the coagulation area that are dependent on the plasma derived products. There's a recombinant, von Willebrand's product, that's under development, but I would predict would be years away.

And so just licensed, for example, was a product to treat von Willebrand's disease with an intermediate purity, Factor VIII. So I think the answer to your question is we're getting there, but that there are still large segments of the bleeding

disorders community that rely on plasma derived products.

And then, of course, I can't see, at least as a hematologist, any time soon having a recombinant IV Ig preparation.

CHAIRMAN BROWN: This -- yes, Peter.

DR. LURIE: Just back to the question of elasticity of the blood supply. And I apologize. This being raised now raises questions for me about the particularly central slide that Dr. Nightingale presented.

Can you put that one up again? Criss crossing lines. I guess I have first a question for you and then, depending on your response, two or three comments on it.

My question is: Are the extrapolations that you present in that slide extrapolations from just the '94 to '97 period, just those two data points, or are we really looking back further in time?

DR. NIGHTINGALE: The slide is what it is; it's a '94 survey and a '97 survey. It comes with confidence intervals that you can see. It is our current best estimate, and it is understood that this is not a prediction within those confidence intervals.

But I think the message in the slide is

that there's not a lot of slack in the blood supply right now.

DR. LURIE: I think the message in the slide is overstated for several reasons. The first is that the Y axis begins at about 11 million units of transfused blood, and so it makes the -- in a section, look rather sharper than, in fact, it is if you extended it all the way down to zero.

The second point is that you've made an extrapolation based just on two points, as you say; and which, in effect, makes it seem as if the two lines are independent of one another. I like to think that the blood transfusion industry, aware of the change between '94 and '97, is, in fact, reacting in some way, presumably by increased recruitment.

So there is a kind of inevitability applied to all of this that doesn't really quite seem right to me.

DR. NIGHTINGALE: Sure. And the -- what doesn't seem right is that past experience will predict future experience, and that is not the implication. I think the implication of the slide is that there are -- there is a bit of concerning information raised at the meeting.

For example, Dr. Williams' survey finding

-- again, preliminary -- that in 1995, 26 percent of donors reported receiving some incentive; in 1997, that 62 percent reported receiving some incentive.

The conclusion that the speakers in the public comment section brought to our advisory committee was, as I stated at the outset, was that there's not a lot of slack in our current blood supply, and attempts to quantitate that, you make your best effort and that's what I think this slide represents.

CHAIRMAN BROWN: Yes, Peter, that's fine.

Thank you, Dr. Nightingale.

This is certainly going to be heatedly discussed in the discussion period this afternoon. And so I'm going to call time for lunch now, but we're going to come back to that and particularly since there are present on this committee now two or three people who were present there.

And clearly this is an important issue. And we'd like to thrash it out as thoroughly and satisfactorily as possible, and we will.

I'm going to reconvene at 1:30 rather than 1:45. That's 45 minutes. 1:30.

(Whereupon, the proceedings recessed for lunch at 12:45 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:42 p.m.)

CHAIRMAN BROWN: This afternoon's program will begin with several presentations as a part of the open public hearing.

And Bill, did you have anything that you wanted to say about the public hearing part?

DR. FREAS: Nothing other than the fact that we do welcome comments from the audience. And this your opportunity, if you're not on the agenda, to come forth and express your views to this committee.

CHAIRMAN BROWN: Yes, there have been several speakers who have given the FDA notice that they wanted to make a short presentation. And in general, as I recall from past meetings, these presentations should be limited to five minutes.

DR. FREAS: That is correct.

CHAIRMAN BROWN: The first speaker from the Armed Services Blood Program, who you've already heard from earlier this morning, is the Director of this blood program, and it's Captain Bruce Rutherford.

CAPTAIN RUTHERFORD: Good afternoon.

The Department of Defense would like to thank you for allowing us to offer public comment.

I am Captain Bruce D. Rutherford, Medical

Service Corps, United States Navy, the present Director of the Armed Services Blood Program.

On 5 February, 1999, Dr. Sue Bailey, the Assistant Secretary of Defense for Health Affairs, forwarded a letter to Vice Admiral David Satcher, Public Health Service, the Surgeon General of the United States.

In that letter, Dr. Bailey expressed her opposition and the opposition of the Surgeon Generals of the Army, Navy and Air Force on deferring individuals as blood donors based on "perception" of a "possible" risk of transfusion transmission of the agent for "new variant" CJD.

There has not been a single case, repeat, single case of transfusion transmitted new variant CJD or classical CJD reported in the world in more than 55 years since transfusion of blood products became widely accepted as a treatment regime.

In November of 1991, the Department of Defense issued an advisory recommending that individuals participating in Operation Desert Storm be deferred as blood donors after a number of Desert Storm troops were identified with cutaneous and visceral *Leishmania tropica*.

Knowing that *Leishmania donavani* was

transfusion transmissible, and now knowing the extent of infection rate of the "at risk" population, the DOD decided to defer those individuals as blood donors who participated in country in the Persian Gulf.

It was not until December of 1993, or two years later, that the DOD stopped asking leishmaniasis related questions of its blood donors. The cessation was due to a concentrated effort by the military health system in identifying an extremely small number of infected individuals and the follow-on screening questions' ability in identifying an extremely small number of donors with symptoms where leishmaniasis could have been a possibility.

However, a study in the survivability and infectivity of viscerotropic *Leishmania tropica* in human blood donors from ODS participants was later shown to support our concern and was published in the American Journal of Tropical Medicine and Hygiene in 1993.

Transfusion transmission by Leishmania species was a known, not theoretical. We know the calculatable risk of being injured in a car accident, yet millions of individuals a day drive their cars with hundreds of thousands being injured per year and tends of thousands killed each year.

It is the same with airplanes, lightening and other activities.

In theory, anything is possible. I remember back a few years ago when the Institutes of Medicine came out with this HIV report. Yes, hindsight was better, but that has always been true.

I think in this case we have hindsight, 55 years of hindsight. We do not need to institute a UK deferral policy which will only lead to further crippling of our nation's blood supply and more product shortages.

However, what we do need is a concerted research effort by federal and civilian entities to develop human virus-free or non-human products to replace the majority of products that we presently use.

We need Hemoglobin-Based Oxygen Carriers presently in clinical trials moved through the regulatory process at a faster pace. We need better hemorrhage control products such as fibrin or non-fibrin based bandages.

We need more recombinant clotting factors produced in transgenic herds, yeast or bacteria. We need to move away from 80 years of collecting blood.

Thank you.

CHAIRMAN BROWN: Thank you, Captain Rutherford.

Are there any questions that any of the panel would wish to address to Captain Rutherford?

The next presentation will be by Kay R. Gregory of the American Association of Blood Banks.

MS. GREGORY: Good afternoon.

I'd just like to come up here rather than try and fix that microphone to my height.

The American Association of Blood Banks is the professional society for over 9,000 individuals involved in blood banking and transfusion medicine and represents roughly 2,200 institutional members including community and Red Cross blood collection centers, hospital-based blood banks, and transfusion services as they collect, process, distribute and transfuse blood and blood components and hematopoietic stem cells.

Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. For over 50 years, the AABB's highest priority has been to maintain and enhance the safety of the nation's blood supply.

The association operates a wide array of

programs to meet the safety priority and is proud to have played a key role in ensuring that the nation's blood supply is safer today than ever before.

The AABB appreciates this opportunity to comment on the potential deferral of donors who have traveled to Great Britain as a means of reducing the theoretical risk of transmission of nvCJD through transfusion of blood and blood products.

The AABB wishes to reiterate its previous position stated at the last meeting of this committee that any measures taken to decrease a theoretical risk must not impact safety by decreasing the availability of the blood supply.

The AABB points out that classical CJD has been the subject of intensive study and notes that current opinion is moving toward a position that transfusion does not transmit this disease. AABB recognizes that data from classical CJD cannot be extrapolated to new variant CJD.

Nevertheless, there are no scientific data to support deferral of donors for new variant CJD. AABB considers it very important to continue to gather and assess data about new variant CJD and was pleased to be able to participate in the survey you heard about earlier today to determine the magnitude of

donor loss should donors be deferred based on travel to Great Britain.

In December, when you met last, this committee recognized that 11 percent of donors, as estimated by AABB and other presenters, would not be tolerable. And you asked for more data to evaluate the impact of imposing different deferral criteria on blood availability.

The AABB would like to call your attention to recent data obtained from the National Blood Data Resource Center on current trends in blood donation and utilization, and you've heard this already this morning. Data obtained from the 1998 blood collection and utilization survey indicate that in 1997 12.6 million units were collected and 11.5 million units were transfused.

For allogeneic units, 93 percent were transfused. Between 1994 and 1997, total blood collections decreased by 5.5 percent, while the total number of whole blood and red cell transfusions increased by 3.7 percent during the same period.

Extrapolating recent trends, the National Blood Data Resource Center predicts that demand will exceed supply by the year 2000 if no changes in deferral criteria are applied. Therefore, even with

no changes in deferral criteria, it is becoming increasingly difficult to maintain an appropriate level of supply.

Spot shortages during holiday periods and during the summer will be even more difficult to alleviate. Any new deferral criteria for donors will decrease the number of donations available. Thus, a policy that defers even a very small percent, such as one to two percent, of available donors will have a detrimental effect on blood availability.

Furthermore, donors deferred for travel to Great Britain would, of necessity, be replaced at least in part by first time donors, a population which has shown to have higher behavioral risk and a higher incidence and prevalence of infectious diseases known to be transmitted by blood.

Therefore, it is possible that the change in the donor base that might occur as a result of donor deferral or travel to Great Britain might increase the risk of transmission of other known or unrecognized transfusion transmitted pathogens.

Another issue that merits consideration is the potential psychological impact of deferring donors who have traveled to Great Britain. A person who is excluded from donation based upon concerns of

transmitting nvCJD may react by becoming anxious about whether he or she might develop nvCJD at a later date.

This is especially worrisome, in that the risk is theoretical, there is no short term intervention or resolution available for the donor, and there is no intervention that can be taken on the donor's behalf to alleviate such concerns.

In conclusion, AABB notes that there is no evidence that nvCJD is transmitted by blood transfusion. There are no cases of nvCJD in the United States. It is unknown whether travel to Great Britain correlates with exposure to or infection with the agent of BSE.

And there is no evidence that any proposed criteria will decrease the theoretical risk of acquiring nvCJD from transfusion. In contrast, there is good evidence that even a one to two percent loss of donors due to new deferral criteria will have a significant impact on blood availability and, hence, on the safety of those transfusion recipients who cannot tolerate a delay in receiving blood products.

The country should contemplate nvCJD deferral criteria only when it is apparent that such a policy would improve blood safety more than the loss of donors and the associated decrease in blood

availability would compromise blood safety.

Thank you.

CHAIRMAN BROWN: Thank you, Ms. Gregory.

The word theoretical has been used many, many, many times this morning and will continue to be used, and it's being used correctly. I'd just point out that, for ten years, between 1985 and 1995, the risk of new variant CJD from BSE was also theoretical.

The next speaker is Dave Cavenaugh from the Government Relations Committee of Ten Thousand.

MR. CAVENAUGH: I'm the government relations person at the Committee of Ten Thousand. The organization is the Committee of Ten Thousand.

CHAIRMAN BROWN: Yes, that's fine. Thank you.

MR. CAVENAUGH: Okay, COTT, which is the Committee of Ten Thousand, is gravely concerned about the industry logic favoring UK donors over additional U.S. replacement donors even with the survey, and even with the lack of data on paid and unpaid high volume pheresis donors.

This morning's discussion showed a glaring omission in the analysis to date of the impact of excluding well paid, highly educated, non-incentive provided pheresis donors in addition to the larger,

understood group of paid pheresis donors.

We've heard quite a bit in terms of the studies and in terms of some of the questions about the likely blood borne nature of this never documented entity of prion and its ability to be transmitted by blood.

There's a perceived link between new variant and beef that's been raised based on proximity, but the BSE classical CJD link should not be forgotten. It should be entertained at the minimum. Living in the United Kingdom in the late '80s seemed to be a major factor, for example.

What was it about living there, that's proximity. Both statistic presenters showed clear risk of new variant in the blood, not even enlarging the scope to include classical CJD. There are no nv cases in the U.S., but plenty of classical -- arguably, much more than the one in one million rate alleged.

Just ask CJD Voice, the patient-family support group which spoke before you 18 months ago. Small then, its numbers have mushroomed. Something is getting transmitted. Can it all be through beef? But most disturbing is the recent news confirming a second mutated form of prions also causing death in under a

year.

This doubling of the number of ways prions can be malformed with fatal results raises our concern levels considerably. The explanation that it is spontaneous sounds like an early catch all. With an entity so new, so unknown and so dangerous, the committee should be providing every protection possible, not bowing to arguments of relative risk.

Thank you.

CHAIRMAN BROWN: Thank you.

The fourth presentation will be by Dr. Michael Busch, who is a member of the Blood Safety and Availability Committee and Scientific Director of Blood Centers of the Pacific.

DR. BUSCH: Yes, thank you. I'm happy to be here and to share a little bit of context because my concern and reason to come to the meeting was to try to put a broader perspective to a focused deferral.

And I think we've learned in the past that focused deferrals can have consequences, and both political and safety consequences. And I just want to share a broader context to these discussions that I hope you'll consider.

There are many ways that we can sort the

donor base toward improved safety, and many of these have been considered over time. And what I've tried to do on these next three slides is just summarize the kinds of donor sorts that have been considered in terms of improved safety.

We have allogeneic and autologous donors at present. For example, autologous donors, their blood is not allowed to be given to other people. There has been great controversy over the years as to the relative safety of directed donors, and you heard today about the potential increased safety of apheresis donors.

Many of these relative safety issues have actually not been recently analyzed carefully. The frequency of donors, the concept that first time donors are higher risk I think is now well established that they're probably two to three fold higher in terms of incidence of the major transfusion transmitted viral infections.

In contrast, among repeat donors, there's a kind of old saw that the more frequently a person gives, the safer. In fact, recent analyses from the REDS group has indicated that the more frequent donors are actually no safer than less frequent donors; and further, that actually apheresis donors are no safer

than frequent whole blood donors.

So some of these theoretical benefits, I think, are not borne out by data. There's good data on regional risk. And for many viruses actually, you can look at the United States and look at different collection regions.

The southeast U.S. versus the midwest, for example, dramatically different: 10 to 30 fold different rates of risk incidence. Collections at mobile sites, at high schools, colleges, etc. versus other sites, urban versus rural.

There's now good data coming forward that show that there's significant relative safety to donations given in different regions. There's a major focus now on incentives. Should we be paying donors to give more frequently or are there other types of payments such as giving donors time off work?

I think Alan Williams' recent data from the REDS survey group shows that actually time off work is a significant predictor of denied risk behavior. So the kinds of characteristics that -- donation related.

Then we can go on to demographic characteristics and I'll show some -- a little bit of data from this, and I think this was distributed to

the committee. But there are dramatic -- significant differences in risk, and particularly the incidence rate of new HIV and other major viral infections distributed by these demographic characteristics.

And I think Alan also showed that the British donor deferral would impact differently on different groups. Again, I'll show some specifics on this. But in general, race ethnicity -- there are some highly significant correlates. The more educated donors are, the lower the incidence.

There's risk associated with country of birth. And just to recall for you the major outcry that occurred over deferral of Haitian donors, and currently there's still in effect a deferral of sub Saharan African donors.

So just the broader context that these geographic-based deferrals have been implemented in the past. Really travel history is what we're focused on now. In the past, there remained deferrals for malaria. There have been intermittent deferrals for travel to HIV risk areas, and now the consideration of British deferrals.

Obviously medical history and behavioral history and surrogate tests are other deferral criteria. Just a little bit of data to illustrate

some of these points. And we're focused here on incidence. Actually, these numbers would be much more dramatic if we talked about prevalence.

Prevalence reflects lifetime accrued exposure to an agent, but the risk of blood is predominantly due to window phase. And therefore, most of our interest in relative risk for established agents for which we screen relates to the frequency of new infections or incidence.

And what you can see actually is some examples of how these potential sorts may be beneficial for one agent and actually detrimental for another. For example, for HIV there's a higher, but not significantly higher, incidence in males than females, but there is a highly significantly increased incidence for hepatitis B in males to females.

On the other hand, both HCV and HTLV are higher incidence in female donors, probably related to secondary sexual transmission from injection drug use. So, what might seem like a safer group of donors for one virus are, in fact, a higher risk subset for another virus.

If you look at age, pretty much across the board there's a age related higher incidence rate in younger donors, but then as donors age, they are less

at risk of being exposed to these agents. Now, as you're aware, the older donors tend to be the better, well off donors who can travel.

As Alan indicated, a British donor deferral would actually bias towards exclusion of older donors and result in the needed replacement with younger donors.

Education is really probably a reflection of socioeconomic status. And again, there is a lower risk of infection with better educated donors pretty much across the board. The one exception is if you focus on high school donors, you need to focus on the younger high school donors who are still high school students versus older individuals who only completed high school.

And once you do that sort, you pretty much see a consistent decline across all viruses with the higher the level of education, the lower the risk of infection with these agents. Again, this is an example where the donors who you're seeing indicate a history of prolonged travel to Britain are the better educated donors, so on offset would occur in replacing those donors.

Race/ethnicity is actually one of the most startling predictors of incidence. Just one example

here, hepatitis B surface antigen with a much higher incidence in black, non-Hispanic and Hispanic donors than in Caucasian donors.

Obviously many of these deferrals are not either practical due to the need to have an adequate blood supply, or ethically or socially acceptable. There's been discussion about exclusion for transfusion. And in fact, in France they've recently implemented exclusion of previously transfused patients from giving blood.

In fact, if you look at prevalence, the prevalence of all these viruses is higher in previously transfused patients, but that's because their risk of acquiring these infections from transfusion predated the introduction of screening.

So now that we're screening the blood supply, this slide just shows from REDS again that the rate of new infections is no different in transfused and non-transfused people. So an exclusion based on history of transfusion will have no beneficial effect with respect to current agents for which we're screening.

If there's an agent that may have been transfused in the past, theoretically there could be a benefit of excluding those donors. But one must be

aware that about seven to eight percent of all blood donors have been transfused in the past.

So an exclusion of transfused donors, somewhat like British donors, would have an incredible impact on blood availability with really, I think, a negligible and non-quantifiable benefit in terms of safety.

I included in the distribution a manuscript that we published a few years ago which actually focused on what was at the time a major controversy. The age deferral issue came up because donors, particularly whole blood sector donors, were later developing classical CJD.

Those reports were coming to FDA, and FDA was taking the position that these products needed to be recalled and/or not distributed, and it was having a huge impact on the availability and financial issues around blood banking.

So what it led to was a sort of knee jerk reaction, well let's just exclude older donors because most of these CJD cases are occurring in older donors. And what we were able to show in this paper and pretty much undermine that policy was that actually the exclusion of the older donors would result in an increased risk; that donors over 50 had a two to

tenfold higher incidence, higher risk than younger donors.

And that, as a consequence, if one were to exclude all donors either under 50 or under 60, you would increase the risk of the blood supply for these known transmissible agents by ten to 20 percent. And I think this was a significant factor in the decision by the blood organizations to not implement this policy and by FDA to eventually reverse that recall policy.

Now, the last point I want to make is that -- is alluding to the impact on donors. And I think until very recently, we've not had data to quantify what notifications to donors that they're deferred indefinitely or permanently on the grounds of non-specific test results or deferral policies has on these individuals.

And recently, the REDS group conducted a survey called the REDS Donor Notification Survey where about 4,000 donors who had been deferred due to test results, various ALT, anti-CORE, false/positive results for various markers were surveyed and asked about the impact of these notifications -- the effectiveness of the notification message and the impact.

And just a few selected results, I think, illustrate that a large proportion of these donors who were being given data that we think is pretty definitive -- we're convinced these donors are not infected.

We've done extensive testing and further testing, and many of these donors are brought up for follow up, additional testing. And they're basically being given a message that you're not infected with this virus, but unfortunately you had some results that are leading us to have to permanently defer you.

And what you can see here is that about 80 percent of these donors, equally split between a lot and a little, indicate confusion when they're initially notified of these results. And the survey actually was conducted in general about five, seven years after the notifications.

And you can see that many of these donors remain confused years later. Again, there's -- about 50 percent of these donors are indicating they're still confused about the meaning of those original notification results, although most of them now are a little less confused over time.

They also indicate a high level of anxiety with about 40 to 50 percent of these donors indicating

that they were very, very emotionally upset when they were told of these results, and another 40 to 50 percent -- 40 percent or so indicating they were somewhat upset.

As with the earlier data, when you ask these donors are they still emotionally upset, this number drops to about half of that level. But many of these donors remain concerned and upset and confused about the meaning of these permanent deferral messages in the absence of any mechanism to reinstate them.

And finally, many of these donors, even though again our message was one of reassurance, have subsequently sought doctors' advice on what to do about this. And unfortunately, in the case of new variant CJD, I don't think we'll be able to give doctors much advice other than trying to reassure these donors.

Coincidentally, I just received a couple letters that I distributed to the committee during the break that are actually from donors that just wrote to my CEO just in the last day.

And I'd ask you to glance at those letters because I think they really point out the intense, you know, emotional experience that individuals go through when they are told they can no longer give blood, many

of them after having, you know, became dedicated donors and feeling that a good, you know, meaningful component of their lives had been giving blood.

And the impact of these false notifications on these donors and the failure of a mechanism to allow these donors to be reinstated and appropriately reassured that their own health and that of their families is not at risk I think is an important consideration as you consider a policy that would impact a very large number of individuals.

Thank you.

CHAIRMAN BROWN: Thank you, Dr. Busch.

I have a question or two for you before you leave. I would imagine that if a statement were crafted that was a little less blunt, it might take some of the emotional backlash out of this.

In other words, instead of sending a note saying "sorry about that, but you're permanently deferred, you'll never be able to give blood again" -- which is unrealistic in the present context. If it were decided to exclude a proportion of British donors, one could send a note saying "you are temporarily excluded from giving blood for the following reason," and put a little paragraph in there why the position was taken.

It's not complicated, complicated. Until such time as we know that this doesn't pose a risk, then we will exclude you, but we will not exclude you permanently. The same thing, I am sure, is going to happen with the screening questions that currently exclude recipients of growth hormone and dura mater recipients.

These are not going to be permanent categories of exclusion. That's the first point.

And the second is that -- did I understand you correctly at the beginning of your speech to say that the data indicates that there is no difference in the risk of having any of these other transfusion related agents between professional donors, volunteer donors, apheresis donors, first time donors and multiple repeat donors?

Did I understand that correctly or did I miss a beat?

DR. BUSCH: Why don't I do the second one first. Yeah, no, there is a quantifiable, increased risk among first time compared to repeat donors. But within the repeat, volunteer donor sector -- so these are the volunteer donors -- although classically people always felt that the more frequently you give, the safer you are and that apheresis donors who are

giving weekly, this kind of special, more committee donation program, are safer than whole blood donors, as we've begun to do analyses in the REDS group with huge databases to try to quantify and validate that, we've been unable to validate that.

There does not appear to be an increasing safety margin as donors give more frequently. This is all data from the volunteer donor sector.

CHAIRMAN BROWN: So, in other words, if you've given twice, beyond that it's a plateau?

DR. BUSCH: That's correct, --

CHAIRMAN BROWN: Okay.

DR. BUSCH: -- that's what our data indicates.

In terms of the first issue, you know, the concern -- from a blood bank operational perspective, that's pretty much what we used to do. We used to tell donors you're, you know, temporarily deferred; that there's a potential that we'll be able to reinstate you down the road.

What that results in is donors frequently calling back and saying "what's happened, where do I stand with this." Eventually, you know, the FDA has in the past come forward with reinstatement programs that allow for donors to go through follow up testing

a year later, for example, that allows them to be reinstated.

In fact, those programs pretty much universally across the country are not operationalized, one, because they're frequently reversed as new tests come in and new questions arise. They're quite onerous in terms of the required testing.

But in addition, they're a regulatory catastrophe. Because if, by chance, eventually a donor who was reinstated gets implicated in another problem, immediately, you know, the FDA comes into your office and the first thing they look for is where's your donor reinstatement records.

And they want to go through those records and verify that those donors were completely, properly reinstated. So, for a variety of reasons, the truth is that donor reinstatement does not occur in this country, with very rare exceptions.

And this is even for agents for which there are FDA approved reinstatement programs. So for these reasons, practically at this point -- and, you know, what's the difference between an indefinite deferral, a temporary deferral?

These are very subtle and often non-