I've ever been on because there are simply inadequate data upon which to base a decision. For myself, in the absence of data suggesting or, rather, documenting risk, I cannot vote yes based on assumptions, perceptions, possibilities, uncertainties, theoretical risks, and potential risks.

On the other hand, there are tangible measurable data that deferral of any percentage of donors, whether it's half, one and a half, two percent, will lead to replacement by donors by a small proportion of donors that are at increased risk for measurable diseases such as hepatitis B and C. So I vote no.

CHAIRMAN BROWN: Dr. Leitman votes no. Dr. Prusiner?

DR. PRUSINER: I would like to vote yes, and I would like to say I have 23 points that I want to go through.

(Laughter.)

DR. PRUSINER: I only want to say very quickly that I don't think that economics and the availability of donors is a reason to vote yes or no in this. I think that the economy has a way of solving these problems, and I think that will happen. I think the real problem here lies that we have a very

imperfect data set, and we're dealing with a disease which is universally fatal. This is really the problem that we face.

CHAIRMAN BROWN: Dr. Prusiner votes yes. Dr. Roos?

DR. ROOS: I think we're dealing with a situation in which we have no evidence of any transfusion that has transmitted either classical or new variant Creutzfeldt. And we have a situation where there are risks involved with blood transfusions that the donors accept at this point.

That is, we were informed about -- I guess about 14 percent of individuals do donate blood that have I guess the recipients. About 14 percent of individuals that donate blood have some risky behavior. And maybe I might include living in UK part of that risky behavior.

And so I kind of accept this as, at the moment, acceptable risk for donated blood and I am awaiting evidence to prove that there is more danger involved. So I'm voting no here.

CHAIRMAN BROWN: Dr. Roos votes no. Dr. Belay?

DR. BELAY: I'm concerned about two issues. The first one is the studies that showed the

presence of the new variant CJD agent in lymphoreticular tissues. And the second concern I have is the absence of evidence against blood-borne transmission of new variant CJD. The kind of data that's available for classic CJD is not available for new variant CJD, so I vote yes.

CHAIRMAN BROWN: Dr. Belay votes yes. Dr. Lurie?

DR. LURIE: Really, what we're doing is balancing one risk against two others. The two risks are the problem of the replacement donor, which is not zero but it is probably very small, given that we're only talking about one, two perhaps, percent replacement of donors here, depending on what happens in B if we get that far.

The second has to do with the diminution in the blood supply itself. And, again, there are scenarios available to us under B that allow us to minimize that. So we really have, on the one hand, two small risks that can more or less be quantified, and on the other hand we have another risk, which may itself be small, but if we are wrong could be very, very large. And that's really the benefit -- the risk benefit calculation that we're making.

For me, there remain too many

uncertainties, and so I vote yes.

CHAIRMAN BROWN: Dr. Lurie votes yes. Dr. Hoel?

DR. HOEL: Yes. I'm changing my vote from last time, and I'm going to vote yes, mainly because of what I see in the epidemiology data of the cases in England and the modeling work. I think this needs to be monitored further to see how it comes in because the risks could be quite large, and so I would vote yes.

CHAIRMAN BROWN: Dr. Hoel votes yes. Dr. Bolton?

DR. BOLTON: I believe that there is insufficient documentation of the risk at this time. And in light of that, I can't -- I don't think that the information warrants changing the current policy. I vote no.

CHAIRMAN BROWN: Dr. Bolton votes no. Dr. Nelson?

DR. NELSON: Well, this is a pretty difficult vote. Last time I voted no, and I'm going to vote no again, although I am -- really, it's disturbing that there is no really good data at this point.

And I am impressed with a comment that was

made earlier, and that is that there is an experiment in the UK of many people who have been exposed to UK donors over a period of many years. And I am somewhat reassured that there have been no cases, and I'm also reassured with the quality of the epidemiologic surveillance and data from the UK.

I think that that has been well done, carefully done, and presumably it will continue to be closely monitored. You know, if a single case had occurred, we would really need to change our policy immediately. That's number one.

But the other problem I have is if I voted yes, then I would have to make a decision on 1B. And the only --

(Laughter.)

DR. NELSON: -- the only reasonable decision on 1B would be to remove -- to exclude all donors who had lived in the UK. I see no basis for any arbitrary decision. Once you go down that route, then you have to exclude anybody from the UK or who visited the UK or Ireland during this period. I don't see any alternative.

CHAIRMAN BROWN: Dr. Nelson votes no. Dr. McCullough?

DR. McCULLOUGH: I agree with Susan. This

is one of the most difficult groups I have had to deal with. I'm impressed by the epidemiologic data. I'm also impressed by having sat through in 1983 and 1984 discussions of there ain't been a case reported yet, and also that we are concerned about the impact on the blood supply.

And possibly also, I'm influenced by having been the fodder for congressional hearings and 60-minute expose on things that might have been done differently at some of those times. So I'm going to vote yes. I have tremendous confidence in the blood systems of this country that they will be able to -- not easily -- respond if changes are made.

CHAIRMAN BROWN: Dr. McCullough votes yes. Dr. Brown votes yes. Dr. Ewenstein?

DR. EWENSTEIN: Yes. I'm impressed by the modeling data. I believe that we have biologic data as well as at least the potential epidemiology coming out of England to suggest that this is a new disease and on that basis should be handled with a lot more caution, because we don't have the comfort that we have with the long-standing classical CJD. And so I'm going to vote yes.

CHAIRMAN BROWN: Dr. Ewenstein votes yes. Dr. Detwiler?

DR. DETWILER: I'm going to vote yes, because with these diseases, a long incubation and the lack of a pre-clinical screening test, that the day you find out there is transmission you're already years too late, and you can't easily clean up the problem. And I think they found out that even with the human transmission because that was based on there is no theoretical -- or it's only a theoretical risk until 1996.

CHAIRMAN BROWN: Dr. Detwiler votes yes. Dr. Piccardo?

DR. PICCARDO: I would vote yes because all of the data from classical CJD cannot be extrapolated into the new variant.

CHAIRMAN BROWN: Dr. Piccardo votes yes. Dr. Williams?

DR. WILLIAMS: I'm going to vote no. I think that this is truly a balancing act, and it's a tradeoff between a known problem, I believe related to the blood supply, and the problems that may follow from a reduced supply and the perception of a risk of new variant CJD.

And I completely agree that an experiment is going on right now. Those data are going to come in, and, obviously, there is going to be close

attention paid to those data, and that surely this committee and FDA will respond should information indicate that we need to take another look at the issue.

CHAIRMAN BROWN: Dr. Williams votes no. Dr. Hollinger?

DR. HOLLINGER: I'm voting no also, for the same reasons that have been addressed. I think there is -- by doing something now doesn't mean that everything is going to be turned around and you don't have to worry about it, if you do have a long incubation situation and one can wait to see if there is some risk down the line, and I think we do have those things going on -- natural and experimental -- in England. So I'm voting no.

CHAIRMAN BROWN: Dr. Hollinger votes no. Ms. Harrell?

MS. HARRELL: Okay. Sitting next to my ex-learned colleague --

(Laughter.)

MS. HARRELL: Okay. I'm voting to be prudent, and I think that this will buy us time to get the data in and have it analyzed from the UK. But right now, we don't have time, and so I vote yes.

CHAIRMAN BROWN: Ms. Harrell votes yes.

Dr. Cliver?

DR. CLIVER: No.

CHAIRMAN BROWN: Dr. Cliver votes no. Dr. Burke?

DR. BURKE: This is a balancing act, and I can -- there are measurable negatives here. In the face of a theoretical, I vote no.

CHAIRMAN BROWN: Dr. Burke votes no. Dr. Tramont?

DR. TRAMONT: I vote yes.

CHAIRMAN BROWN: Dr. Tramont votes yes. Twelve yes. Nine no. Well, at the least, Dr. Epstein can come away from the day with the understanding that he has not been given a mandate.

(Laughter.)

DR. FREAS: Can I just make a comment? I did verify the count. There are 21 voting people at the table. Dr. Roos is a non-voting participant. And the total does add up to 21.

Excuse me. I apologize. Dr. Rohwer is --

CHAIRMAN BROWN: I don't have to ask Bob what he would have voted, had he been allowed to vote.

(Laughter.)

CHAIRMAN BROWN: But I will if you'd like to put it on the record.

This is simply a question to Bob, since he's at the table. Were his vote to be counted, what would it have been?

DR. ROHWER: I'll use this soapbox opportunity.

CHAIRMAN BROWN: Uh-oh.

(Laughter.)

DR. ROHWER: I am very concerned that we may be facing the grave possibility of an epidemic of new variant CJD, an epidemic that, if it occurs, could be made much worse through the mechanism of interspecies transmission, such as would occur through blood products. But I recognize the real risks of insufficient supply.

However, I am impressed by Dr. Donnelly's warning that if the feed ban in the case of BSE had been delayed just one year, the epidemic would have been vastly worse than it was. And, therefore, I feel we should take whatever opportunities for implementing mitigating measures that we can that do not simultaneously jeopardize the supply unduly.

So I recognize that what we have -- the opportunity we have here is very, very imperfect, but I feel like it is possible to do something, and we should do it.

CHAIRMAN BROWN: Jay, you wanted a recount, or just a reexpression?

DR. EPSTEIN: Just a reexpression.

CHAIRMAN BROWN: Okay. The vote on question 1A is 12 votes yes, nine votes no. Therefore, the committee is obliged now to consider what deferral criteria might be recommended. And presumably, based on the evidence, the only deferral criteria that are offered us that make any sense are duration of residence in the UK.

DR. LURIE: It's also duration and when.

CHAIRMAN BROWN: Yes. But it's -- the "when" will be 1980 to 1999.

DR. LURIE: As long as that's established, I would agree with that. But --

CHAIRMAN BROWN: Yes, that's the only information we have. In other words, the question is: have you lived in the UK during the period 1980 to 1996? And, if so, how long? And the answers and the distribution of those answers has already been presented to the committee.

Do I hear an opening bid on time? Larry?

DR. SCHONBERGER: I'd like to point out that all cases to date in the UK have lived there for at least four or more years, and been potentially

exposed. And most of them, as I understand it, have been there for 14 years or more during the 17-year period.

The one that I'm more concerned about for the shorter exposure -- and I tried to get more details about it; maybe Bill has some more information on it -- was supposedly a person who was a -- who claimed to be a vegetarian since late 1985, at least that's how it was reported in the newspapers.

And Will has not contradicted that, although he indicated to me that there is vegetarians and there is vegetarians, and he was not totally convinced that this particular individual might not have been exposed later. But that person would have certainly been there through the 19 -- I'm getting a note here. The point would be that she would have been exposed, then, during the '80 to '85 period.

I just bring that out. Meanwhile, I'm sure there have been many travelers to the UK. There have been military people from the U.S. that have visited shorter periods of time. We haven't seen any cases in that group yet, but at least it offers me some sort of rationale, again not to totally eliminate risk, but to have some basis for modifying the risk. And, of course, I'm also concerned of the impact on

blood supply.

So I was thinking in terms of a three- to five-year category; that is, as I understand it, that would include about .7 percent of the donors in the United States, and that probably would be tolerable to the blood system in the United States and get well over half the person days of risk and give us some modification of the risk in the United States.

Obviously, if we start getting cases among travelers in shorter times, we would need to tighten that even further.

CHAIRMAN BROWN: Just for the committee's information, there has also been one case in France that never visited the UK.

DR. SCHONBERGER: That's right. There is one case in France that never visited it, so that illustrates the point that our whole -- this whole policy is not 100 percent protection. I think that point was raised by Rohwer, and so on.

CHAIRMAN BROWN: Well, to the extent that we have not imported British beef products for the past 10 years, it is.

DR. HUESTON: More than that. We haven't imported it for more than that.

CHAIRMAN BROWN: Right. Maybe ever since

-- you know, 15 years. So, whereas, 20 percent of beef that the French eat, or ate, was imported. In other words, the French case -- clearly, the implication is the French case got their disease because of exposure to British beef. That doesn't happen here.

Stan?

DR. SCHONBERGER: Yes. I was referring to, obviously,, the protection that one gets from the screening criteria.

CHAIRMAN BROWN: Yes.

DR. SCHONBERGER: Those screening criteria that we can come up with is -- that's practical --

CHAIRMAN BROWN: Going to be total.

DR. SCHONBERGER: -- can give you 100 percent protection. We're just trying to make a judgment where to draw the line.

CHAIRMAN BROWN: Exactly.

DR. SCHONBERGER: I just -- you said to throw out an idea. That was my proposal.

CHAIRMAN BROWN: Okay. Well, that's fine. Stan?

DR. PRUSINER: I have a slightly different analysis of this, but not much. If one looks at Alan Williams' handout, the second -- third-to-the-last

page of slides, and put up this graph which I thought was very informative on residual variant CJD risk --

CHAIRMAN BROWN: Is that the zoom-in slide?

DR. PRUSINER: Right.

CHAIRMAN BROWN: The one that --

DR. PRUSINER: Exactly.

CHAIRMAN BROWN: -- goes from one year to one week?

DR. PRUSINER: Exactly.

CHAIRMAN BROWN: Okay.

DR. PRUSINER: That's the one. So I think if people look at that slide -- I mean, we can start thinking about everything from one week to one and a half years with this slide. And I think everybody -- most people, I would argue, at this table would argue that one week is too severe, and this creates something which is intolerable for the blood supply.

And it may well be that even one month or three months do that. I'm not sure. I'm not totally convinced of that.

But clearly, by six months, if one looks at that, and then one looks at this handout that Alan Williams provided us that was not stapled, if one picks the number six months, then of all of the -- if

you look at the cumulative person days, then almost 95 percent of the cumulative person days are eliminated by picking a figure of six months.

So I would think that for purposes of discussion --

CHAIRMAN BROWN: Where is six months on the handout?

DR. PRUSINER: So it's five to eight months.

CHAIRMAN BROWN: That's the one?

DR. PRUSINER: Yes.

CHAIRMAN BROWN: Okay.

DR. PRUSINER: Right? So that's 84 percent.

CHAIRMAN BROWN: So you're suggesting a split between the one to four above and the five to eight below.

DR. PRUSINER: Yep, something on that order. I'm zeroing in on between six months and three months. This seems to me to be a very reasonable way to achieve a 90 percent reduction in risk without making a huge dent on the blood supply.

CHAIRMAN BROWN: Okay. Further comments?

DR. ROHWER: I would second that.

DR. EWENSTEIN: I would also second that.

I was just going to ask for clarification whether we were talking about cumulative time in the UK, and I know that was an issue, or whether we're talking about longest stay.

CHAIRMAN BROWN: I think we were talking -- you were talking cumulative, huh?

DR. EWENSTEIN: If we're going to use the person years, and it's cumulative --

CHAIRMAN BROWN: I think we shouldn't also forget the table before. It's on the flip side of that. In fact, it's exactly backing the figure you just talked about -- blood resources lost by deferral of donors. And even at a year there, the loss is one and a half percent.

DR. PRUSINER: That's right.

CHAIRMAN BROWN: Yes.

DR. PRUSINER: And it just rises very modestly if we pick six months, or even three months. It's when we start getting down to a month that things start to get very -- the curve starts to change dramatically.

CHAIRMAN BROWN: Other comments? Bob?

DR. ROHWER: The only comment I'd have was -- is the 1980 to 1996. I am not comfortable myself with limiting this deferral to 1996. I mean, I would

run it right up to the present. I don't feel like we've come close to really proving that the way that new variant -- the new variant cases get this disease is from eating contaminated meat.

And, in fact, my understanding of the CJD surveillance unit attempt to do so is that they couldn't make that correlation. And there are some very peculiar things about this disease; namely, that it seems to affect young people preferentially, suggesting that there may be some risk factor that babies or infants are exposed to that we just haven't identified yet that puts them at special risk for this disease.

And because we haven't nailed it down, I don't think we should consider necessarily that the exposure is over. We don't know where it's coming from. And I would extend it right up to the present until we know better.

CHAIRMAN BROWN: It occurs to me that a vote on question 1B could be a very heterogeneous vote. We could have people saying one to three days versus five to 17 years. It seems to me that procedurally the best way may be to work up from the least restrictive to the most restrictive, and get a consensus on each separate category.

So that if we had, for example, every -- since we're obliged to work with some sort of a cut, if we can get everybody who is voting to agree on at least eliminating five to 17 years, then we can move on and see where the threshold is when the committee decides enough is enough. Susan?

DR. LEITMAN: Those of us who voted no on question 1A are now faced with an illogical option of telling --

CHAIRMAN BROWN: No, you can abstain.

DR. LEITMAN: Oh.

CHAIRMAN BROWN: No, I'm serious. I understand that that puts you folks in a very difficult position because you would prefer that this not be done at all. And I think you have the right to abstain.

Or if you want to be very logical, you have the right to stick with the least restrictive, if you want to kind of still have an influence. I mean, wouldn't you agree, these are the sort of two options that you have?

DR. LEITMAN: Yes, I agree.

CHAIRMAN BROWN: Stan?

DR. PRUSINER: Could I make a suggestion, and then maybe we could accelerate all of this? If I

make a motion of four months, which really splits this point that I've been talking about, and if there's a second, and then there's a vote, we don't have to do this systematically. If we can't come -- if you're unable to call the question because there is too much discussion, then we have to do it your way.

CHAIRMAN BROWN: Peter?

DR. LURIE: Maybe a simpler one. If we apply to this the same method of analysis that Alan applied to the blood donors, we could just have a descriptive account of where each of us individually thinks the cutoff should be, and then FDA will know that X percent of the 17 voting of us -- you know, what the cutoff would be.

CHAIRMAN BROWN: That's not a bad idea. Jay, would that be satisfactory, do you think, as kind of an accelerating compromise to this question? You would then have at least -- well, you'd have raw data rather than pooled than pooled data.

(Laughter.)

DR. EPSTEIN: Well, we can deal with being advised either way. It's easier for us if there is a consensus of the committee. If there isn't, then I think what we default to is a set of opinions.

CHAIRMAN BROWN: Okay. Let's do it this

way, then, Peter. Why don't we go around the table. Those who wish to commit themselves to a suggested cutoff, we'll take the cutoff down. And it's conceivable that the first round will get a consensus. And if it doesn't, we can then decide whether we want to continue to try and reach a consensus.

Yes? Is it very relevant? Okay.

MR. COMER: Thank you, Chairman. I just thought that it was relevant just to make a comment from the sort of risk perspective of what you all are going to -- just about to be deciding on or voting on. We're talking about a very uncertain risk.

If we're going to make any risk reduction strategy, then it has got to be a significant risk reduction to make any sense at all. And, in my mind, the minimum that you could be talking about that would be a significant risk reduction will be at least a factor of 100, because if it -- talking in factors of 50 percent, even 90 percent is actually not a very significant risk reduction when we talk about all of the uncertainties that we have.

And I suspect that when you start talking about really significant risk reductions, we're getting into the area -- and I agree completely, I think, with what Kenrad Nelson said -- where we have

impracticality.

That possibly does not help your decision making, but I think it is just relevant that what we need to have, if we're doing this, is a significant level of risk reduction, if it's worth doing anything at all.

CHAIRMAN BROWN: Paul?

DR. HOEL: What we're talking about is risk benefit here, not risk reduction.

CHAIRMAN BROWN: Let's change the order. Dr. Tramont?

DR. TRAMONT: Four months.

CHAIRMAN BROWN: Four months? Dr. Burke?

DR. BURKE: Is it either/or four months or can we give another option?

CHAIRMAN BROWN: Any time cut that you would like to vote on or --

DR. BURKE: Six months.

CHAIRMAN BROWN: Six. Dr. Cliver? And, again, you needn't vote if you would prefer not to on this question.

DR. CLIVER: Abstain.

CHAIRMAN BROWN: Mrs. Harrell?

MS. HARRELL: Six months.

CHAIRMAN BROWN: Dr. Hollinger?

DR. HOLLINGER: I guess eight -- greater than five years.

CHAIRMAN BROWN: Dr. Williams?

DR. WILLIAMS: This seems rather arbitrary, but I'd say a year.

CHAIRMAN BROWN: Dr. Piccardo?

DR. PICCARDO: Four months.

CHAIRMAN BROWN: Dr. Detwiler?

DR. DETWILER: Four months.

CHAIRMAN BROWN: Dr. Ewenstein?

DR. EWENSTEIN: Six months.

CHAIRMAN BROWN: Dr. Brown? One year. Dr. McCullough?

DR. McCULLOUGH: Six months.

CHAIRMAN BROWN: Dr. Nelson?

DR. NELSON: Six months.

CHAIRMAN BROWN: Dr. Bolton?

DR. BOLTON: Five years.

CHAIRMAN BROWN: Dr. Hoel?

DR. HOEL: Six months.

CHAIRMAN BROWN: Dr. Lurie?

DR. LURIE: Six to 12 months.

(Laughter.)

CHAIRMAN BROWN: So six would be the cutoff, right?

DR. LURIE: That's fine.

CHAIRMAN BROWN: Dr. Belay?

DR. BELAY: One year.

CHAIRMAN BROWN: Dr. Roos?

DR. ROOS: One year.

CHAIRMAN BROWN: Dr. Prusiner?

DR. PRUSINER: Four months.

CHAIRMAN BROWN: Dr. Leitman?

DR. LEITMAN: Greater than or equal to five years.

CHAIRMAN BROWN: Dr. Hueston?

DR. HUESTON: One year, between '85 and '95.

CHAIRMAN BROWN: Dr. Schonberger?

DR. SCHONBERGER: Three years.

CHAIRMAN BROWN: Was that one of the cuts, three?

DR. SCHONBERGER: Yes, three years or greater.

CHAIRMAN BROWN: Okay.

DR. SCHONBERGER: Or greater than two years.

CHAIRMAN BROWN: Greater than two?

DR. SCHONBERGER: That looks like what the --

CHAIRMAN BROWN: It depends actually on what you're working from. But yes, so that would be three to five, that would be --

DR. SCHONBERGER: Yes, three or more. If you've got three --

CHAIRMAN BROWN: Okay.

DR. SCHONBERGER: -- years, you're out.

CHAIRMAN BROWN: Well, the most hits were on six months -- seven. But that is not a quorum, or it's a quorum but it's not a majority. So there were eight votes favoring a cutoff of one year or greater. There were seven votes for six months or greater. There were four votes for four months or greater. And I think that's 19 -- that's -- I'm sorry, there was one abstention, that gets us up to 20.

DR. LEITMAN: You're counting those who voted greater than five years as voting greater than one year, but --

CHAIRMAN BROWN: Just for the moment. I'm just tallying this out. I'm not trying to cheat you, Susan.

(Laughter.)

CHAIRMAN BROWN: Specifically, there were -- if you want the exact tallies, there were three votes for greater than five years. There was one vote

for greater than three years. There were five votes for greater than one year. There were seven votes for greater than six months. And there were four votes for greater than four months. I still may be missing one. And there was one abstention. So that's 21.

Have we any suggestions from the committee as to where to -- how to proceed now?

DR. LURIE: Yes, the median is six months. The median is six months.

CHAIRMAN BROWN: The median is six months. Is that a good consensus, Jay? No? Yes?

DR. EWENSTEIN: You could just ask for one year versus six months at this point.

CHAIRMAN BROWN: Well, Jay has the raw data, and we've already got a statistician that has calculated the median.

(Laughter.)

DR. EPSTEIN: Which also adds up to a majority.

CHAIRMAN BROWN: And it also -- so I think we've done enough, frankly, on this question. And I would like to go directly to question 2A. Can we immediately, without further discussion, proceed to a vote on question 2A?

All right. Larry?

DR. SCHONBERGER: Yes.

CHAIRMAN BROWN: Oh, I thought you were answering me.

DR. SCHONBERGER: No.

CHAIRMAN BROWN: That's a vote, is it? Okay. Question 2A, Schonberger votes yes. Dr. Hueston?

DR. HUESTON: No.

CHAIRMAN BROWN: Hueston is no. Dr. Leitman?

DR. LEITMAN: No.

CHAIRMAN BROWN: Leitman is no. Dr. Prusiner?

DR. PRUSINER: Yes.

CHAIRMAN BROWN: Prusiner is yes. Dr. Roos?

DR. BELAY: He just walked out.

CHAIRMAN BROWN: A pitstop. Dr. Belay?

DR. BELAY: Yes.

CHAIRMAN BROWN: Dr. Belay votes yes. Dr. Lurie?

DR. LURIE: Yes.

CHAIRMAN BROWN: Dr. Lurie votes yes. Dr. Hoel?

DR. HOEL: Yes.

CHAIRMAN BROWN: Dr. Hoel votes yes. Dr. Bolton?

DR. BOLTON: No.

CHAIRMAN BROWN: Dr. Bolton votes no. Dr. Nelson?

DR. NELSON: No.

CHAIRMAN BROWN: Nelson votes no. Dr. McCullough?

DR. McCULLOUGH: Yes.

CHAIRMAN BROWN: McCullough votes yes. Dr. Brown? Yes. Dr. Ewenstein?

DR. EWENSTEIN: Yes.

CHAIRMAN BROWN: Dr. Detwiler?

DR. DETWILER: Yes.

CHAIRMAN BROWN: Dr. Piccardo?

DR. PICCARDO: Yes.

CHAIRMAN BROWN: Dr. Williams?

DR. WILLIAMS: No.

CHAIRMAN BROWN: Dr. Hollinger?

MS. HARRELL: Pitstop.

(Laughter.)

CHAIRMAN BROWN: Did he leave a vote on this at all? Probably not. 2A? Dr. Hollinger would -- Dr. Hollinger votes no. Ms. Harrell?

MS. HARRELL: Yes.

CHAIRMAN BROWN: Dr. Cliver?

DR. CLIVER: No.

CHAIRMAN BROWN: Dr. Burke?

DR. BURKE: No.

CHAIRMAN BROWN: Dr. Tramont?

DR. TRAMONT: Yes.

CHAIRMAN BROWN: Exactly the same tally, 12 to nine. Boy, consistency. Oh, well, good for the Chairman. Dr. Roos is -- all right, 12 to eight. So whatever Dr. Roos' vote will be, we're obliged to consider question 2B.

Should we proceed directly to find out if the committee feels that precisely the same criteria should be applied to question 2A as were applied to question 1B -- 2B and 1B, identical? Therefore, I can simply ask the question. The question is: shall we apply the same criterion for question 2B as we applied for question 1B? Larry?

DR. SCHONBERGER: Yes.

CHAIRMAN BROWN: Will?

DR. HUESTON: No.

CHAIRMAN BROWN: Susan?

DR. LEITMAN: What are we voting on?

(Laughter.)

CHAIRMAN BROWN: The vote on the first

question, question 1A, which was decided to proceed and suggest a cutoff, those cutoff numbers were a variety. And the vote now is to determine whether the committee agrees to use the same cutoff on this question with respect to pool products.

DR. LEITMAN: So is each timed vote -- or each interval voted on by each committee member? We're voting on whether we --

CHAIRMAN BROWN: That's right.

DR. LEITMAN: -- use the same interval --

CHAIRMAN BROWN: That's right.

DR. LEITMAN: -- right now?

CHAIRMAN BROWN: That's right. That's right.

DR. LEITMAN: So if I say yes, then I'm saying it's whatever my interval was --

CHAIRMAN BROWN: Exactly. Each individual is --

DR. LEITMAN: Could you please frame the question?

DR. PRUSINER: No, that doesn't make any sense, Paul.

CHAIRMAN BROWN: What?

DR. PRUSINER: That doesn't make any sense. Let's just find out if everybody wants six

months or not, right around the table. Six months is the number we agreed upon in 1B, right?

CHAIRMAN BROWN: That was not -- that was not my understanding at all.

DR. LEITMAN: No. We gave the raw --

CHAIRMAN BROWN: We gave the raw data.

DR. PRUSINER: I thought we had a consensus.

CHAIRMAN BROWN: Well, no, there was no single number that had a majority.

DR. EWENSTEIN: Can we rephrase it another way, then? Can we just -- because I think it will be very difficult to have two different criteria, even though Dr. Epstein had come up with a solution to that. So can we at least recommend that whatever the FDA adopts in 1B they be consistent in 2B?

CHAIRMAN BROWN: That's the sense of what I had, that the criteria that we are -- that each person suggested for question 1A, individually that they would use the same criteria for question 2B.

DR. EWENSTEIN: And it can be rephrased to just say that the same criteria should be used in both situations.

CHAIRMAN BROWN: Yes.

DR. BURKE: I'm not sure that -- it will

be impossible to achieve a consensus. I think we might achieve a consensus on 1B if you were to revote on six months, yes or no.

CHAIRMAN BROWN: Well, I think we can. We could have done the same thing on -- actually, on question 1A, but I chose not to. I just think that, you know, for example, Susan would certainly not agree to a yes vote on six months for question 2B.

DR. BURKE: But several of the people who voted one year or four months might switch, and that way we can present with a consensus and then we can actually have internal consistency of a vote for the second -- for 2B.

CHAIRMAN BROWN: Without having it for 1B.

DR. BURKE: Well, I'm saying I think we can at least try to see if we can get 1B, take one more vote to see if we can get a consensus for 1B. If we cannot, then fine.

CHAIRMAN BROWN: Well, let me ask a question to every member of the committee. Would you, given the opportunity, change your cutoff criteria for question 2B? Change it from what you suggested for question 1B? Is there anybody who would say, for example, five years for 1B and three days for 2B? I don't think so.

In other words, is the committee actually -- would the committee be voting the same cutoffs individually for question 2B as they voted for question 1B? If there is any dissent to that, let's hear it.

DR. BOLTON: Paul?

CHAIRMAN BROWN: Yes.

DR. BOLTON: I think that there are really two different issues here. One is whether we are going to try to give a recommendation or this collection of votes for each 1B and 2B, or whether we give them the numbers and allow the FDA to make that decision and then just ask that they make it consistent for both 1B and 2B.

CHAIRMAN BROWN: Yes.

DR. BOLTON: Do you see the difference?

CHAIRMAN BROWN: I don't quite see the difference. I think we're both asking for the same thing in a slightly different way. Is there anybody else on the committee that would like to give the Chair guidance on this question? How would you like to phrase the vote on 2B? Stan would like to phrase it, "Let's take a vote on six months."

DR. EWENSTEIN: I would like to phrase it that we -- that the same criteria be used for 2B as

for 1B.

CHAIRMAN BROWN: Okay. I think that makes sense, and that's what we'll vote on. Should the FDA use the same criteria for question 2B as was or will be used for question 1B? Larry?

DR. SCHONBERGER: Yes.

DR. HUESTON: Yes.

DR. LEITMAN: Yes.

DR. PRUSINER: Yes.

CHAIRMAN BROWN: Dr. Roos, long pitstop. Okay. Dr. Belay?

(Laughter.)

DR. BELAY: Yes.

CHAIRMAN BROWN: Dr. Lurie?

DR. LURIE: Yes.

CHAIRMAN BROWN: Dr. Hoel?

DR. HOEL: Yes.

CHAIRMAN BROWN: Dr. Bolton?

DR. BOLTON: Yes.

CHAIRMAN BROWN: Dr. Nelson?

DR. NELSON: Yes.

CHAIRMAN BROWN: Dr. McCullough?

DR. McCULLOUGH: Yes.

CHAIRMAN BROWN: Dr. Brown? Yes. Dr. Ewenstein?

DR. EWENSTEIN: Yes.

CHAIRMAN BROWN: Dr. Detwiler?

DR. DETWILER: Yes.

CHAIRMAN BROWN: Dr. Piccardo?

DR. PICCARDO: Yes.

CHAIRMAN BROWN: Dr. Williams?

DR. WILLIAMS: Yes.

CHAIRMAN BROWN: Dr. Hollinger?

MS. HARRELL: Pitstop.

(Laughter.)

CHAIRMAN BROWN: Someone better get after these two people. He had a no on 2A. Okay.

(Laughter.)

CHAIRMAN BROWN: Okay. Oh, that's right. Dr. Hollinger left. Dr. Harrell?

MS. HARRELL: Yes.

CHAIRMAN BROWN: Mrs. Harrell, excuse me. Dr. Cliver?

DR. CLIVER: Yes.

CHAIRMAN BROWN: Dr. Burke?

DR. BURKE: Yes.

CHAIRMAN BROWN: Dr. Tramont?

DR. TRAMONT: Yes.

CHAIRMAN BROWN: Unbelievable. Unanimity. I thank very much the committee for -- excuse me?

DR. ROOS: Yes.

(Laughter.)

CHAIRMAN BROWN: Okay. I am obliged, unfortunately, to depart now, and I'm going to turn the chairmanship over to Dr. Roos for consideration of criteria used for the diagnosis of new variant CJD. And he is eminently qualified to do this as a long-standing clinician with research interest. Dr. Roos?

DR. ROOS: Thanks, Paul. I hope this section goes more smoothly and quickly. I guess -- Bill, are we going to have a presentation? So we're going to have a presentation from Dr. Dorothy Scott on the operational definition of possible new variant case for quarantine of blood and blood products.

Dr. Scott?

DR. SCOTT: Well, I think the committee is relieved to hear that this is not for a vote but only for your discussion and thoughts. So what I want to introduce is just a proposed FDA operational definition of a possible new variant CJD case for the purpose of deciding whether there should be a quarantine or withdrawal of blood or blood products from such a possible case when information is missing that would lead to a firm diagnosis of new variant CJD in a blood donor.

This is just to summarize what has happened previously. I think most people here are familiar with it. That is, in August 1995, and then revised slightly in December 1996, the FDA issued a memorandum recommending deferral of all donors with CJD risk factors from donating that included family history in one or more family members, or if they were pituitary growth hormone recipients or had received dura mater.

And it was also recommended to withdraw all products, including plasma derivatives, if a donor developed CJD, had a positive -- strong positive family history with two or more family members with CJD, was a pituitary growth hormone recipient, or a dura mater recipient.

This was all revised and the revision was announced in late August 1998 by Dr. Satcher. And this revision was based on epidemiologic evidence. It was extensively reviewed, which you've already heard about, or at least has been very much alluded to, would show that there was no evidence so far of any transmission of CJD by blood products.

And this was supported by lab-based scientific evidence which showed at least a diminution of titer of the CJD or TSE agents in processing of

plasma.

So you've already been through this today. Obviously, our concerns about new variant CJD is that there is a lack of experimental data showing whether or not blood can transmit this particular infection, and also we don't know much about partitioning during manufacturing of the new variant agent. In fact, we don't really know anything yet.

In addition, we do know, as Dr. Prusiner has pointed out several times, that the new variant agent is biologically different from the classical CJD agent, so we can't necessarily extrapolate all of the information that we have on classical CJD to new variant.

For example, he talked about the differences in the protein and its behavior, and we also know that there is enhanced expression of the new variant agent in lymphoid tissues compared with CJD. And we don't know much about its virulence or infectivity compared with the classical CJD.

And, of course, we haven't had time to get or enough patients or subjects or transfused people to get the kind of epidemiologic data that we have which tells us that transmission of classical CJD by blood or blood products at worst is rare and may not occur.

So, currently, the diagnosis of new variant CJD is based upon neuropathology, and these are the three most characteristic features -- numerous widespread kuru type amyloid plaques, which obviously can occur in a few other kinds of CJD but are quite common in new variant CJD; spongiform change, which is predominant in certain areas of the brain; and a high density prion protein accumulation, especially the cerebrum and the cerebellum by immunohistochemistry, and tonsillar biopsy may ultimately play a role in this diagnosis as well as analysis of prion glycoforms.

You can't see the top of this, but actually it's in your handout. And what I have there is CDC suspected new variant CJD case definition for use when pathology is not available. In other words, there isn't always going to be a neuropathological specimen to examine, or it might not be big enough, I guess.

And so we do need clinical criteria to try to tell if we have a possible new variant CJD case, and the CDC has developed such criteria and this is mostly based on the findings that are described by the CJD surveillance unit in the United Kingdom.

And I want to point out that this kind of

list is going to be subject to change as clinical and diagnostic methods and experience evolve. However, the current CDC definition -- the suspected new variant CJD case would include all nine of the following -- current age, and, of course, we're talking about in donors for our purposes, but the CDC is also using this kind of definition for their own surveillance.

Current age, if alive, or age at death, less than 55. Since the typical age of a new variant patient is about late 20s, and the typical age of a classical CJD patient is about 65, this is one criteria that is useful. And new variant patients tend to have persistent painful sensory symptoms early in presentation and/or psychiatric symptoms.

I can go into this further if people want to know about it. But there were a couple of articles published in the Lancet from the CJD surveillance unit in September 1997, which goes into this in great detail.

In addition, the patient must have dementia and a delayed development of neurologic symptoms, particularly movement disorders, about a four-month delay. And, again, this is somewhat different from classical CJD in its course. They may

have a normal or abnormal EEG, but not the diagnostic EEG, which is a pseudo periodic sharp wave that's often seen in classical CJD.

The duration of illness should be greater than six months. Again, this is in marked distinction to most cases of classical CJD which average four to four and a half months of duration. Whereas, the new variant case typically is around 14 months duration, although there is a spread.

In addition, routine investigations will not suggest an alternate diagnosis. And this is a criteria, really, for the U.S. There should be history of possible exposure to BSE; that is, consumption of local beef products as resident or traveler to a BSE-affected country.

And there is only two more. No history of iatrogenic exposures that are related to development of classical CJD, and, finally, of course, such a patient, if they had a prion protein gene mutation, it was associated with familiar CJD. That would not fall under -- that would not be a patient that we would worry about new variant CJD in.

Certainly, other criteria may be added, as I mentioned, in particular the CJD surveillance unit is expected to publish something about MRI studies,

looking in great detail at certain areas of the brain which might be very useful in making the clinical diagnosis without neuropathology of new variant CJD.

Well, if we used all of those nine criteria to consider whether or not we should quarantine or withdraw a blood product in a case of -- a suspected case of new variant CJD, we might run into a problem.

And one of the possible problems is that two of these criteria are time-based, so one is the time course of disease greater than six months and the other is that a period of four months should have elapsed before development of neurologic symptoms but after the initial symptoms.

And it's conceivable that a true new variant case could come to our attention where this time has not elapsed. And, secondly, travel history and symptom history might not be available or they might not be very accurate.

So from the FDA point of view, what we have been considering is whether or not to lower our threshold for considering withdraw and quarantine of a product, where we don't even have all of the information needed for the CDC criteria for suspected new variant CJD.

So we have proposed the following that -- and, again, I'm sorry, the heading is missing. But that for such a case to be considered even as a possible, or I should say potential, new variant case, it will be a donor who had a physician's clinical or pathological diagnosis of either CJD or new variant CJD.

And the donor would be young, less than 55 years of age. And, of course, such a donor would not have risk factors for classical CJD. And that's what we would call a possible new variant CJD case. And I should point out that although we would include all three of these criteria, from the point of view of reporting to the CDC, we would want to ask plasma establishments and blood banks to also report donors who were young but had risk factors for classical CJD that came down with disease.

And the proposed actions for possible new variant cases with this low threshold of consideration by FDA for disposition of blood and plasma products -- the actions that we would propose would be an immediate investigation and review by CDC and FDA of all of the available case information, and followed by an expeditious decision by the FDA on a case-by-case basis as to whether blood products from such a patient

should be withdrawn as a precaution.

So just in summary, obviously, this is already built in, that any definite new variant CJD case would result in quarantine and withdrawal of all products. In addition, we're proposing that suspected cases meeting all nine of the CDC criteria would also be quarantined and withdrawn.

And that criteria for possible CJD, the young age, the diagnosis of any kind of CJD, would trigger a rapid investigation followed by an expeditious decision about a precautionary withdrawal and quarantine of material.

So that's what I have, and I open it, then, to discussion or comments.

DR. ROOS: Thanks, Dr. Scott. So we're not asked to take a vote, but just to discuss these issues. Yes?

DR. NELSON: I'm concerned a little bit about the explanation for the age criteria, and I can see that this is very useful because the one thing you do know, when somebody gets sick, you can estimate what their age is. And so that's an easy -- you know, an easy early marker for a possible case that's not classical.

And I assume that probably the reason for

the classical CJD patients being much older is that the incubation period is so long that they probably had an exposure much longer. But as this epidemic -- or as the -- if it's exposure to the BSE agent from the epidemic, it seems like over time this age criteria will probably change, and that the under 55 may no longer be a useful criteria 10 years from now or 40 years from now.

And I just wonder if Larry or anybody could comment on that.

DR. SCHONBERGER: We definitely agree, and it underscores the evolving nature of these diagnoses. All I can say is the age is an excellent and easy criteria for us to use now. All cases, as you know, in the world of new variant CJD have been under age 55. In fact, I think the oldest was -- I think the median age is like 29 or so, 28 at onset and 29 at death. So that's why that particular criteria came into existence.

However, obviously, if the epidemic should change and we should start seeing older cases, then, obviously, we would have to change.

There is some semantic problems. We actually investigate every case under 55. So, in a sense, all cases under 55 in the United States could

be regarded as under investigation or possible. We have not used the word "probable," in part because that's the word they use in the United Kingdom, and they count those cases as amongst the cases of new variant CJD that we count.

The 40 cases in the UK, I think, includes one, is it? One probable? That was a case in a teenager whose brain tissue was unavailable for study. And they indicate that it's too early in the epidemic. Their experience is too small for them to be absolutely sure about that, but they're willing to -- at this point to call it a case.

And I've been told that with these new MRI criteria, and so on, that maybe we'll be able to call cases without necessarily having the tissue, depending on what they find the specificity and sensitivity of those to be. So all cases essentially under 55 right now are under investigation.

Plus, we have established amongst pathologists the concept that any case that has the pathology of new variant CJD, regardless of age, or even regardless of whether they've diagnosed it as CJD, should be reported. And those two would count as new variant even though they are not under 55.

DR. ROOS: Just a quick question, Larry.

What is your timeframe of reporting, or what is the goal here? Obviously, with respect to these new guidelines, you want to identify these cases fairly quickly and make some disposition as far as blood products.

DR. SCHONBERGER: Precisely because we are looking at all cases under 55, I was encouraging FDA to encourage the blood establishments -- or the first to identify these cases at least, and that has been the history -- to report to us any case of CJD under 55.

Once we get that report, it may be very easy for us and very quickly making it -- to very quickly make a determination that we're dealing with, say, a dura mater case or a human growth hormone case. But then, another part of FDA will probably become interested in that.

So we think it's worth the blood establishments reporting all of their cases in donors. There just are not that many CJD cases that are going to occur among donors that the blood establishment is going to be able to identify that quickly. But if they do, we want it reported right away.

DR. ROOS: Just a quick question. So, I mean, how about if this patient donates to some large

blood pool or has donated whole blood? It doesn't go back to the blood establishment. It goes to a neurologist, gets diagnosed, etcetera. What's the timeframe then?

DR. SCHONBERGER: Well, frequently, our experience with the withdrawals -- and I'll use the Utah case as an example as that came out -- we handled that very, very rapidly. But even handling it very, very rapidly, you'll find that huge, huge numbers of recipients were exposed to this donor's blood products.

So the withdrawal program is relatively inefficient, compared to what we just did, which was to get deferral criteria. And I think that's why it was important to try to be preemptive in a sense and have the deferral criteria up front.

The withdrawal procedure, even when you do it very quickly as in the Utah case, I would not encourage people to depend on that for considerable safety. What we will do is we will modify and ameliorate the situation. But it certainly won't eliminate even the majority of the risk.

DR. ROOS: I just think it might be good to publicize these new policies widely to the neurological community, so that they alert you, Larry,

or the FDA quickly. The Utah case, in fact, was kind of a very aberrant case. It could be that there are other cases that get less sophisticated care. And if you really want to identify things in a timely manner, you obviously have to publicize the program and new policies to the neurological community.

DR. SCHONBERGER: Well, let me clarify that the primary group doing the surveillance on this are blood establishments. And if this group wants to recommend that blood establishments, you know, provide blood donors with cards or something that would, you know, speed up any type of reporting, that's possible.

The surveillance that CDC is conducting is not designed for that type of rapid turnaround or rapid identification in reporting. That's another weakness of the system and relying on this withdrawal system for tremendous protection of the population.

DR. ROOS: Peter?

DR. LURIE: My question/concern is whether or not requiring all nine of these criteria is too restrictive a set of criterion. I guess the data question that I have is: of the 30-odd new variant CJD cases in Britain, how many of them have met all nine of these criteria?

DR. SCOTT: Well, could I also respond to

that question?

DR. LURIE: Yes, please do.

DR. SCOTT; I don't know the answer to how many have had all nine of those criteria, but most. However, the CJD surveillance unit has somewhat altered their criteria with time such that the current organization is similar to this but not the same. And most critically, they have gotten rid of the age criteria and added an MRI criteria. But this is not yet published material, and it's very recent. We just got that information on May 31st.

And I think the other thing to mention is that we weren't considering only using all nine criteria. But, really, that's the purpose of the third way, if I can say it, which is to have a very low threshold for identifying even potential cases and then to make a rapid decision on a case-by-case basis.

But what we're anticipating is probably what you're thinking, that not all of those criteria are going to be met, just due to a lack of information, time hasn't passed, we don't have material to analyze. And so I think what we're anticipating is that we would be -- we would err on the side of caution unless investigation showed us that it was most unlikely that this was a new variant

case.

DR. LURIE: I'm still left -- I'm afraid after that answer, it -- which may be the best you can give. I'm still left with uncertainty. I mean, it seems to me that that is a basic question. And if independent of data that are unavailable for the reasons that you point out there are people who do not have myoclonus, or whatever, and they don't have the right time course of disease, etcetera, we might -- and they may be too restrictive.

I think, at a minimum, it would be interesting to find out the answer to that question, and that might inform us better.

DR. SCOTT: Right. I can also tell you that in terms of the course of the neurologic progression, they reported I think it was 14 or 17 patients, and three of them would not have met, for example, that criteria because they got their movement disorders before four months had elapsed.

So you're absolutely right. Likewise, it was the psychiatric. So we would not be using the nine criteria per se in a potential case, as including or excluding the possibility of withdrawal.

DR. ROOS: Yes. I guess I kind of agree with Peter that I might have felt more comfortable if

all of the cases satisfied the criteria of suspected cases, plus others that then turned out not to have new variant.

In other words, you want to throw somewhat of a larger net to take care of a lot of the comers, especially when you only have 40 cases that have presently been identified.

DR. SCOTT: That's right.

DR. ROOS: Yes?

DR. BELAY: I just wanted to say that all of the new variant CJD patients in the United Kingdom meet all of this criteria. In fact, in addition, a certain proportion of classic CJD patients could also meet this criteria, all nine criteria. So by no means this criteria is just specific to new variant CJD.

The only criteria that we added was item number 7, which is a history of possible exposure. Again, even in new variants we get patients that would -- that would still be present, because most of them resided in the UK.

DR. ROOS: Yes, Will?

DR. HUESTON: Three thoughts. One -- if, in fact, a case meets the three -- the three criteria for definite CJD diagnosis, you don't need to go through the rest.

DR. SCOTT: That's correct, yes.

DR. HUESTON: Right. So some of the cases were identified because they met these criteria. They were defined without going through all of the rest of the history.

Point number 2, in terms of the nine -- and I just mentioned to Larry -- for all practical purposes, I think number 7 ought to be simply revised to say, "Resident or traveler to a BSE-affected country." The bottom line -- you do not know what you've eaten.

(Laughter.)

DR. HUESTON: You don't know to what you've been exposed. So it's -- the second thing is it draws -- I think it gives a false sense of security and directs, potentially, attention to the wrong products, because the average person thinks of beef as primal cuts of beef. And that's, at this point, the least likely of the sources of exposure, given meat products.

The third comment is that I personally am very concerned about the proposed -- this criteria of possible new variant CJD by FDA. And I have two major reasons for that. The first is that I see the potential for conflict arising between FDA and CDC,

where FDA is stepping forward or making a pronouncement of possible new variant CJD, and at the same time CDC says, "We're still investigating; you know, it's premature."

And I think that puts the FDA in a very awkward position, and I think an inappropriate -- Larry is telling me that they are investigating 25 --

DR. SCHONBERGER: There's about 25 cases under 55 a year.

DR. HUESTON: So my fear -- here is my fear based on my experience. Item number 2 says, "Donor has physician's clinical or pathologic diagnosis of CJD."

DR. SCHONBERGER: They're not all donors, by the way. Very few of them are donors. Okay?

DR. HUESTON: Okay. Fair enough. But once you get a terminology like this established, my concern is that it's going to spread further, that people are going to say, "Well, the FDA would have called this a possible case."

Number 2 says, "Has a physician's clinical or pathologic diagnosis," it doesn't say anything about the physician. And no offense to my distinguished colleagues, but there are a number of physicians that are simply not in the position to make

a clinical diagnosis or a pathologic diagnosis of Creutzfeldt Jakob. That has not precluded some of these same physicians from making a proclamation.

Third, I think that the public health and the risk communication implications of this are potentially massive. And having been on the firing -- you know, on the other end of trying to deal with these, you know, the press grabbing hold of a case and blowing it totally out of proportion and creating a great deal of concern, I don't see why you need another term.

I think you coordinate with the CDC, you coordinate your investigation when it comes back from a blood collection center that you have a donor less than 55 years of age, where you have some suspicion of Creutzfeldt Jakob Disease. You go through the same CDC workup, and you base -- on a case-by-case basis, you base your decision on that coordination with CDC.

DR. SCOTT: Right. So we would leave those products on the market if the patient hadn't had six months of disease, for example. You see, there has --

DR. HUESTON: I'm suggesting that you do it on a case-by-case basis --

DR. SCOTT: Right.

DR. HUESTON: -- in association with CDC. And you may decide to take action prior to meeting all of those criteria.

DR. SCOTT: Right.

DR. HUESTON: I'm concerned about putting forth yet one more term that I believe will be misinterpreted. It will create more misinformation than it will help clarify the situation.

DR. ROOS: Just so I understand, Will, the term is this possible new variant. So maybe it could just be stated that cases were under investigation at that point, rather than label it potential or possible. And I must say, I kind of thought FDA and CDC were working together on these cases. That was kind of my assumption. Okay. So -- Dr. McCullough?

DR. McCULLOUGH: I have the same concerns from the standpoint of the blood banking system. It isn't clear to me exactly when the process of the market withdrawal begins. But if it starts earlier than the resolution of the case by -- based on the nine criteria, what we have under the proposed criteria is someone that some physician says has CJD and is under 55 years of age.

And if something close to that triggers the market withdrawal, potentially involving very

large amounts of plasma derivatives, and all of that sort of thing, I have a lot of concerns about that. I think those actions need to be much -- to be initiated much farther along in the investigation of the case. So I have the same concerns about these very minimal criteria.

DR. SCOTT: Well, if I could interject -- I think what I intended to convey was that those small, three criteria would trigger an investigation that the FDA would be involved in, but not necessarily a withdrawal.

DR. McCULLOUGH: I'm reassured if you can assure me the FDA wouldn't, from time to time, decide to start things sooner, which could happen, I think.

DR. ROOS: Yes?

DR. EWENSTEIN: I think we should also remember that these patients, whatever their subsequent diagnosis, may be the recipients of products that the FDA regulates, and not just the source of products. And so I think it's important to have a low sensitivity for the -- I mean, we talk about hemophiliacs never having been diagnosed with CJD.

Well, you need a low sensitivity to make sure that you're not missing that sort of thing.

There are, obviously, other groups that are certainly in a high risk in terms of receiving biologic products.

DR. ROOS: I had a question. I didn't see any real criteria used related to the abnormal glycoform of new variant. And it was my understanding that all new variant cases had a specific electrophoretic mobility after the proteinase treatment. And why isn't that one of the definite criteria here?

In other words, if you did a brain biopsy that was normal, let's say, or looked pretty normal, or had, you know, just minimal changes, and you saw this distinctive glycoform, would that be adequate by British standards, or should it be adequate by our standards?

Larry, do you want to --

DR. SCHONBERGER: I don't know of any of the cases that don't have the definite diagnosis criteria -- that don't have that and have the glycoform alone. I've had it the other way around, for example, even with the Utah case. We did it based on a biopsy, and there was insufficient material, as I recall, to get the glycoform --

DR. ROOS: No. I had heard that it was --

it was -- it did not look like a BSE new variant.

DR. SCHONBERGER: No, I'm --

DR. ROOS: On the basis of --

DR. SCHONBERGER: No, I understand that. What I'm saying is we had an inadequate specimen for the glycoform. We were able to get the Type I protein fragment at 21 KV, which sort of ruled out the new variant. But we were not able to get the glycoform pattern, certainly right away. I don't know if he ultimately got it. I don't think he even ultimately got that.

Do you remember that, Ermias?

DR. BELAY: I'm a little concerned about adding this glycoform ratio as a case definition for two reasons. The first one is there is no standardized kind of methods that are being used by different groups. That the group in the United Kingdom -- namely, Collinge group -- would use a different criteria compared with other groups within the United States.

So that part of the, you know, method -- the immunoblotting or the Western Blot method -- has not been characterized or has been -- has not been standardized. And the second concern I have is there are other diseases potentially that could have the

same kind of glycoform ratio. And Dr. Pedro probably can correct me on this. FFI, I think, has been reported to have a similar kind of glycoform ratio also.

DR. PICCARDO: Yes. Let me back up for a second. First, I agree with what you've said. If the standardization of prp res, Western Blotting, is -- it is still under discussion.

So the UK -- Collinge group -- has one classification, up to seven different forms of normal prp while in the UK. In the U.S., basically, there is a Type I and Type II that have been recognized. So that is under intense discussion as we speak right now. So I would not base the diagnosis on that. That's for sure. And even at the pathologic level -- let me see, I had to walk out for a second because I had to get a taxi, but -- so I have to ask you a question. You were talking about that Utah case, and you were talking about the biopsy, right?

So I think at this point in time for the pathologist to make the diagnosis we'll need the full autopsy. I mean, with a small piece of tissue, with a lot of spongiform changes, with plaques, even in that biopsy, even with florid plaques, I would not feel comfortable in making the diagnosis, because you

can have rare forms of sporadic CJD in which you have a lot of spongiform changes.

And if you have a minimal amount of amyloid of plaque there, it will be florid, because it will be surrounded by vacuoles. So I think in order to make the diagnosis of new variant from a pathologic point of view, you need the full autopsy.

DR. SCHONBERGER: Generally, I agree with you. We were able in this instance, however, to show that it was not a Type II protein, but, rather, a Type I, which was -- which gave us hard data that was inconsistent with the new variant as reported in the UK. But generally, obviously, most pathologists are going to want the entire brain to deal with.

DR. PICCARDO: I'm not arguing against. All I'm saying is I think we have to be extremely careful. And the only way to be sure about all of this would be the full autopsy. And then work the -- the ratios, glycoforms, etcetera, etcetera -- I mean, we need more time for that.

DR. ROOS: Larry, the definition of suspected and definite -- this corresponds to the CDC classification at the moment or --

DR. SCHONBERGER: Yes. In fact, they had asked us to come up with this definition, and that's

where that comes from.

DR. HUESTON: It's compatible with the Brits, too.

DR. SCHONBERGER: And it is definitely compatible with the UK, although I'm in fairly regular touch with Rob Will, and he tells me that they are changing their criteria and that's why I was emphasizing that people have to regard these criteria as something in progress. It's a model being made.

DR. ROOS: Good point. Any other questions? Peter?

DR. LURIE: Just to be clear, if any one of these nine criteria is not present for reasons of the examination not being done, like an EEG, or not enough time having elapsed, it will count as if it is, in fact, present, right?

DR. SCHONBERGER: Yes, that's right. We would not count the absence of information as being negative. So that's why if a person is alive at five months, that doesn't -- he hasn't really lived greater than six months, that doesn't rule that case out.

DR. ROOS: But it sounds like the action that might be taken by the FDA in a particular case is done on a case-by-case basis. In other words, we are leaving a certain amount of discretion up to them in

their investigations, which I think at this point is probably appropriate, rather than putting every little detail --

DR. SCHONBERGER: I'm sure if Jay saw that we had five months, and that was the only difference, we'd be withdrawing that blood.

DR. ROOS: Yes?

DR. PICCARDO: I think we have to be very careful and very flexible with all of this. Setting the criteria now I think is good, as a working thing. But I think we have to be extremely careful, because in the unfortunate event in which heterozygotes nv will start developing the disease, they might have a completely different phenotype.

So this is just a work -- in my opinion, this is a working hypothesis, and we've set this criteria and we will have to modify that accordingly. I think that's the way to go.

DR. ROOS: It sounds like we are all in agreement about this being a good template to follow, and that maybe we shouldn't introduce a new term probable or possible Creutzfeldt Jakob, and that the FDA should look carefully and on a timely basis at these cases.

I would suggest that you do publicize

these actions to the neurological community because I think they're the ones that probably are going to have these cases come to them, rather than blood banks specifically.

Yes?

DR. ROHWER: Ray, I just wanted to draw attention again to number 7. It seems to me like while that's very helpful in implicating a case, it shouldn't be an absolute criteria for putting it in this category because it eliminates the possibility of discovering cases which may arise de novo from other causes in our midst -- for example, this Utah case.

DR. ROOS: I agree. If there are no further cases, I guess I'm going to call this session to an end and thank the committee members and other discussants.

Tomorrow morning is?

DR. FREAS: Tomorrow morning we will reconvene at 8:30 in the morning. I ask the committee members not to leave anything on their desks. The hotel may clear off the table tonight, and we do not want you to lose any of your papers. Thank you. See you tomorrow morning at 8:30.

(Whereupon, at 5:43 p.m., the proceedings in the foregoing matter went off the record.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in

the matter of: MEETING

Before: TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

Date: JUNE 2, 1999

Place: GAITHERSBURG, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.