1 inventory to the outflow, and so forth. But it was a
2 crude first cut.
3 We did indeed obtain and are still obtaining
4 monthly data on supply, which went back from some
5 retrospective collection to October of '99. And
6 remember that although our guidance became final in
7 November of '99, the guidance called for
8 implementation within six months, which was not until
9 the end of April of 2000.
10 So the U.K. deferral in most parts of the
11 country went into play in April of 2000. At that
12 point in time, we did indeed have at least monthly
13 monitoring of supply ongoing, and the data which we
14 were actually shown at the January meeting of this
15 committee showed that the supply did remain flat.
16 So that is point one, and point two is that
17 the deficiencies of that model have been recognized.
18 It was a survey that was done at 26 centers, and they
19 were selected so that they could be monitored
20 statistically to represent the U.S. blood supply.
21 However, there were those limitations, and
22 there was a limitation of the periodicity. You know,
23 one month is a long time to look at fluctuations that
24 might go on daily or weekly.
25 That the data were only be received one

1 month later than they were being collected, and that
2 it might not fully represent the U.S. So there is now
3 a second initiative which the Department of Health and
4 Human Services is funding.
5 The original effort was funded ad hoc by the
6 NHLBI, and I believe it was originally a 3 year
7 commitment. There was an extension to continue that
8 funding through December of this year.
9 Now, the second initiative is focused on
10 daily monitoring of inventories in hospitals. That is
11 different than monitoring of distributions from blood
12 collection centers, and the concept is that it should
13 enable us to get one step closer to recognizing when
14 we are in a difficult situation of supplying a
15 hospital in the United States.
16 And I believe that that effort is being
17 brought about through contracts with a number of
18 hospitals. Data will be obtained, I believe, from the
19 majority of the America's Blood Center hospitals, as
20 well as selected other hospitals.
21 And that the contracts were supposed to be
22 in place by the end of July. I am not in a position
23 to comment on whether that is actually going to occur,
24 but there is some optimism.
25 So we are moving toward putting in place

1 systems that can monitor the availability of the
2 blood, as well as the utilization of the blood, and
3 also look at the health of the inventory.
4 Is there a 3 day stock, a 2 day stock, a one
5 day stock, or an out of stock situation, and how does
6 that stratify according to the blood groups, because
7 as we have heard the relative proportion of
8 collections and demand is not the same for the
9 different blood groups.
10 There tends to be a shortage of Group "O"
11 for which you have to over collect all groups to have
12 enough Group "O" on hand. So that is what is
13 happening. Now, it is still short of having the kind
14 of system that Dr. Klein is calling for, which is a
15 comprehensive on-going, full established, and funded
16 monitoring system.
17 We are still talking about efforts that are
18 ad hoc, and will have a limited lifetime pending a
19 decision to create some form of permanent monitoring
20 system, either run by the government or run by the
21 private sector, and somehow funded by one or the
22 other, or both. We are not there yet.
23 But we do have these government funded
24 efforts as I say, and the one that has been looking
25 since October of '99 at blood made available, and the

1 one that we hope will start up soon after July to look
2 at hospital inventories, and that is just where we
3 stand today.
4 DR. NELSON: Jay, is there a plan to also
5 look at plasma products, IVIG, in the same way?
6 Because we have heard comments here from hemophilia
7 organizations and others needing special products. Is
8 it feasible to do that than to have to do it later?
9 DR. EPSTEIN: It has been mentioned, and
10 Steve is now at the microphone, and perhaps can give
11 a more up to date answer.
12 DR. NIGHTINGALE: I think that Jay
13 summarized the situation very well. What we are
14 trying to do is to do two things, and these are right
15 now actually on direct orders from the Secretary.
16 One is to get the thing started as quick as we can,
17 and number two is to make better as quick as we can.
18 The Secretary has been made aware of the
19 need to monitor the plant and the supply, as well as
20 the blood supply, and where we are with the monitoring
21 of the supply side as Jay said is that we have monthly
22 data on both blood and plasma collections that we have
23 had for about 2 or 3 years.
24 We had a meeting of our advisory committee
25 in April, where we discussed some ways where those

1 could be improved, and one of the items that we are in
2 continued discussions right now is how we can improve
3 those models, and where are we going to get the money
4 for them.
5 I believe that is an answerable one,
6 however. And having established with limited data on
7 supply, we are now moving to the first phase of
8 measuring demand, which is measuring blood on the
9 shelves or in the refrigerator of the purchasers.
10 And the first purchasers will be the
11 hospitals. Very briefly, we are going to spend
12 $250,000, and $150,000 on 29 sites, and $93,000 on a
13 secured website.
14 I sent out 18 of the 27 contracts yesterday
15 afternoon, and the website contract yesterday
16 afternoon, and expect to have the remainder at least
17 in the mail by the close of business on Monday, and
18 those would be verbal commitments.
19 There are several people in the room who
20 have made verbal commitments to participate in this
21 system. We hope to begin collection as early as July
22 2nd.
23 When we get the system up, and not until we
24 get the system up, but hopefully we will have
25 everybody on July 30th, and that will be the time when

1 I hope to initiate discussions about the plasma
2 supply.
3 And one of the ideas that has been floated
4 is that there are 36 Children's Hospitals in the
5 United States, and they use a lot of gamma globulin.
6 They use a lot of clotting factors, and their
7 equipment people we need to talk to.
8 We need to talk to the patient service
9 organizations. We need to talk to the middle man, and
10 we need to talk to FFF, and a couple of their major
11 distributors.
12 This is not rocket science stuff. The
13 rocket science actually is getting consensus on how to
14 collect or how the material should be collected, and
15 when one should initiate a process, and when one
16 should get started.
17 And my own view, which has prevailed for the
18 moment, is get started and try to make it better, and
19 the first public data which we are going to try to
20 make it better is on August 24th of this year, when
21 the Advisory Committee on Blood Safety and
22 Availability will meet to review the progress to date,
23 and to make recommendations.
24 However, recommendations between now and
25 then are more than welcome. My name is Steven

1 Nightengale, and my direct line is (202) 690-5558.
2 CHAIRMAN BOLTON: Dr. Belay, and then Stan.
3 DR. BELAY: I support collecting this kind
4 of data on the blood supply situation in the United
5 States and also blood utilization, but unfortunately
6 we have to make a decision today in the absence of
7 this data.
8 But there is one data that we can use and
9 that is presented to us today, and that is that we
10 don't have to be a genius to figure out what would
11 happen to the blood supply in the New York area,
12 because we have been told that 25 percent of the blood
13 supply is obtained from you.
14 In addition, the other foreign policy based
15 on the travel history may impact on the New York area
16 for an additional 10 percent, and probably bringing
17 the total percentage to 35 percent.
18 And that is a substantial amount, and so
19 this is data that we can use to make a decision today
20 as we go along through the process.
21 CHAIRMAN BOLTON: Stan.
22 DR. PRUSINER: What I wanted to -- well, I
23 am happy that we just heard about all of the things
24 that are in place and going forward, and all the
25 caveats of this, but it is my understanding -- and I

1 would like Jay to respond to this again.

2 That besides the 2.2 percent loss that the
3 committee created when it set this six month policy in
4 the U.K. from 1980 to 1996, there was another event
5 going on that had to do with the American Red Cross,
6 and it had nothing to do with this.

7 And which then created a shortfall of
8 approximately 3 percent for the whole country. So the
9 blood supply was flat, with an actual reduction in
10 donors during that time of 5.2 percent. And maybe,
11 Jay, you can explain it better than I can.

12 DR. BELAY: You have stated it accurately
13 that the Red Cross implemented a change in the donor
14 screening process, moving from the ear lobe stick for
15 the hematocrit to a finger stick.

16 That resulted in a loss within the Red Cross
17 system of about 6 percent of the donors, and given
18 that there are 44 or 45 percent of the whole system,
19 that is a loss in the range of 3 percent for the
20 system as a whole.

21 Within the same year the 2.2 percent loss
22 for the entire system was incurred consistent with the
23 FDA recommendation on the U.K. deferral. So we do
24 believe there was something in the neighborhood of a
25 5.2 percent loss nationally occurring over that

1 approximately year or year-and-a-half period.

2 And the evidence from the supply monitoring

3 contracted for with the NBDRC was that supplies stayed

4 flat. Additionally, Jackie, you are here and can tell

5 us, that the Red Cross reported that within their own

6 system they were able to offset their aggregate a plus

7 percent loss, with increased collections somewhere in

8 the neighborhood of 9 percent, actually resulting in

9 a net increase, if that is a correct statement,

10 Jackie.

11 So we do know that losses of that magnitude

12 have been offset and in recent history. But the

13 question is how readily can it be done again, and what

14 kind of resources would be needed to make that a

15 success nationally, and what do we want to see in

16 place first before we incur the deferrals.

17 CHAIRMAN BOLTON: Okay. One more. Steve.

18 DR. PETTEWAY: Thanks, David. I would just

19 like to follow up on what Dr. McCurdy has suggested

20 relative to blood and plasma, and the differences

21 between blood and plasma.

22 And there is a significant difference in

23 overall risk relative to blood products and the

24 administration of blood products, and the development

25 of plasma derived products with processing and

1 potential removal.

2 And while it maybe somewhat complicated, it

3 is not unreasonable to potentially look at the risk at

4 the donor level, or the donation level, differently

5 between the two because of the way the products are

6 produced, and the risk reduction during production

7 before they go into patients.

8 CHAIRMAN BOLTON: Would someone representing

9 the blood collection agencies like to again respond to

10 that, or is it -- my sense is that it is a nice

11 argument, but that as a practical matter the

12 collections are done -- will probably be done under

13 some uniform set of standards.

14 DR. KATZ: There are going to be more

15 deferrals than there are now, and I think there is

16 nobody that doesn't recognize that. You give us

17 enough money and enough time, and we will make it up.

18 I mean, I want to make that clear. Enough

19 money and enough time, and we will get the donors. I

20 mean, we use payday advertisements in my center, and

21 we have an enormous advertising budget and for us it

22 works.

23 And one of the reasons that we have an

24 advertising budget is that recovered plasma is a nice

25 byproduct that somebody gives us a bunch of money per

1 liter for.

2 So take it away, and I want to know where

3 the resources come from. We are talking about money

4 and time.

5 DR. PETTEWAY: Not to push the debate

6 further, but remember that in the plasma industry that

7 we plasmapherese. So our point of collection and what

8 we collect, and what we fractionate is really

9 different from blood and recovered plasma.

10 CHAIRMAN BOLTON: Okay. Stephen.

11 DR. DE ARMOND: I guess I am the only one

12 who hasn't said anything this afternoon. It seems to

13 me though that -- and I have listened to this

14 tremendously being a rookie member on the committee,

15 and there is lots of tremendous insight, but I don't

16 see where it is going.

17 And I don't get to a bottom line, and each

18 insight doesn't tell me how I should vote. And as I

19 see this process, it is an evolving process of

20 recommendations about balancing the risk of variant

21 CJD and blood products, versus the risk of causing

22 deaths or morbidity by not having blood products.

23 And the three choices that we are given, and

24 possibly a fourth, have their pluses and minuses, but

25 it is clear that both the FDA and the ARC changes in

1 the policy from 6 months ago in response to real data
2 that tells us what there is an increase in variant CJD
3 in Great Britain, which is disturbing.
4 And with some projections, depending on
5 incubation time, going out to a hundred-thousand
6 people or more. So there is some reason to become a
7 little more stringent in the way that we deal with
8 that.
9 Also, the increasing BSE or the more
10 awareness of BSE in a variety of countries and on the
11 European continent also has raised the alert. And
12 basically what we need is new data, and I am sure that
13 we are going to meet in six months, and we will have
14 a lot of new data.
15 We certainly need to have testing of blood
16 and blood products to see what the real risk is. We
17 need to know more about variant CJD in these other
18 countries.
19 And as for the choices that we have, it
20 looks like it is between not doing anything, which
21 again with the increasing data suggesting that there
22 is increasing variant CJD tells us that maybe we have
23 got to be a little more stringent.
24 We have got a choice then between ARC and
25 FDA, and ARC, I think, goes too stringently. They get

1 a good reduction in risk, but at a very high cost in
2 terms of blood.
3 The FDA gets virtually the same reduction in
4 risk, and at half the effect on the blood supply. And
5 yet I don't know how to say that we can split up
6 Europe into different parts. It seems to me that the
7 FDA has done a relatively decent job in trying to
8 piece this whole thing together.
9 And so unless I can hear somebody say that
10 definitely we have to split Europe into its individual
11 parts, and vote on each one of them, I think we are at
12 -- I have not heard anybody really say that we are
13 going to have anything greatly different from the
14 three choices that exist.
15 CHAIRMAN BOLTON: Let me freeze things here
16 for a moment, and give you my sense, and that is that
17 we are close to being able to resolve this question,
18 and that in fact if we were to look at Option Number
19 3, the FDA proposal, there are probably 3 out of the
20 5 lines that we could get a sense that we are in
21 agreement on.
22 And I would just like to informally do that
23 by a show of hands, and that in the second item under
24 Option 3, "To defer donors who spent any cumulative
25 period of 3 months or more in the U.K. from 1980

1 through the end of 1996," would all those in favor of
2 that item just raise their hands?
3 (A show of hands.)
4 DR. FREAS: There are 17 voting members at
5 the table, and 12 voted in favor.
6 CHAIRMAN BOLTON: So, 12 out of 17, and this
7 is informal, but those who would vote no on that to
8 defer donors, would they please raise their hands?
9 (A show of hands.)
10 DR. FREAS: Let me go by names, because we
11 do want this for the transcript. That would be Dr.
12 Burke, Dr. Williams, Dr. Prusiner, Dr. Cliver. So,
13 four no's.
14 CHAIRMAN BOLTON: And this is informal.
15 DR. CLIVER: If it informal, why do you need
16 our names for the transcript?
17 DR. FREAS: We do use these transcripts in
18 subsequent deliberations and it is nice to have a name
19 with a vote.
20 CHAIRMAN BOLTON: And abstentions?
21 DR. FREAS: Shirley, you were a no-vote?
22 MS. WALKER: Yes, because I thought that the
23 argument for just restricting it period was a good
24 one, instead of using or splitting the country in
25 half.

1 CHAIRMAN BOLTON: Oh, no. This was just
2 considering this second item. This is just 3 months
3 or more in the U.K., versus the current recommendation
4 of 6 months.
5 MS. WALKER: That's fine. I misunderstood.
6 The 3 months will be fine.
7 CHAIRMAN BOLTON: So that would be another
8 yes vote.
9 MS. WALKER: That will be a yes.
10 CHAIRMAN BOLTON: Stan.
11 DR. PRUSINER: I think there is an important
12 modification to that data that we are skipping over,
13 and that is that I think I would like to just see you
14 take another straw vote and just change 1996 to the
15 present.
16 That to me is very problematic. We were
17 discussing this, and I don't know exactly where you
18 are headed, but I am just throwing that out to you if
19 you want to do it later.
20 CHAIRMAN BOLTON: Well, we can take that
21 straw vote, but I would do that in addition to what we
22 just did.
23 DR. PRUSINER: Okay. Fine.
24 CHAIRMAN BOLTON: So those that would accept
25 deferring donors for 3 months in the U.K., from 1980

1 through the present, raise their hands if they are in
2 favor of that?
3 DR. FREAS: There are nine yes votes.
4 CHAIRMAN BOLTON: And those who are opposed
5 to that?
6 (A show of hands.)
7 DR. FREAS: Dr. Burke, Dr. Williams, Dr.
8 Lurie, Dr. Cliver, Dr. Priola, Dr. Belay, Dr.
9 Ferguson.
10 DR. LURIE: I misunderstood. I need to
11 change my vote.
12 CHAIRMAN BOLTON: To yes or no?
13 DR. LURIE: No, it should be through the
14 present.
15 CHAIRMAN BOLTON: Through the present?
16 Okay. Are there abstentions? I think that is 10
17 then, and one abstention.
18 DR. FREAS: One abstention.
19 CHAIRMAN BOLTON: Now, I will try to make
20 this clear. On the subpart of Option 3, to defer
21 donors who spent more than six months on a European
22 Department of Defense base from 1980 through the end
23 of 1996, with or without segregation of north versus
24 south, and on the general concept, those that would be
25 in favor of including that, would they raise their

1 hands? In favor of Item Number 3, Option 3?

2 (A show of hands.)

3 CHAIRMAN BOLTON: I will read it again. To
4 defer donors who spent more than six months on a
5 European Department of Defense base from 1980 through
6 he end of 1996, or from 1980 through 1990, if all
7 exposure after 1990 was on Department of Defense bases
8 north of the Alps.

9 DR. DE ARMOND: And that is essentially the
10 same as your original --

11 CHAIRMAN BOLTON: Yes, that is the original.

12 DR. DE ARMOND: -- from six months or more.

13 CHAIRMAN BOLTON: That's right. That's
14 current.

15 DR. EPSTEIN: I'm sorry, but there is no
16 current deferral for exposure on military bases unless
17 they happen to be in the U.K. What we are saying here
18 is if there was exposure on any European base. So
19 this would be a totally new policy.

20 CHAIRMAN BOLTON: Okay.

21 DR. EPSTEIN: All right.

22 DR. PICCARDO: Can we make it to the
23 present?

24 CHAIRMAN BOLTON: Yes, we can make it to the
25 present, but let's get the first vote as it stands.

1 I just want to have some sense of whether this is
2 acceptable or not.
3 So as it stands, reading Item 3 under Option
4 3, will all those who are in favor of that raise their
5 hands?
6 (A show of hands.)
7 DR. FREAS: There are 11 yes votes.
8 CHAIRMAN BOLTON: And those voting no?
9 (A show of hands.)
10 DR. FREAS: The no votes are Dr. Burke, Dr.
11 Williams, Dr. Priola, Dr. Nelson. Four no votes.
12 CHAIRMAN BOLTON: Any abstentions?
13 DR. FREAS: There is one abstention, Dr.
14 Cliver.
15 CHAIRMAN BOLTON: And finally, and probably
16 the easiest one, and that is to defer any recipient of
17 a blood transfusion in the U.K. from 1980 to the
18 present. All those in favor, raise their hands?
19 (A show of hands.)
20 DR. FREAS: There are 17 votes. It is a
21 unanimous 17 votes in favor.
22 CHAIRMAN BOLTON: So Peter was correct in
23 that, and that that is a no-brainer. But the only one
24 perhaps. So I guess my sense of being close -- well,
25 no, those are the three easy ones.

1 The problem that we have now are Items 1,
2 certainly, and possibly Item 5. So, Item 5 may be the
3 easiest. Dr. Ewenstein had suggested that we might
4 recommend that the implementation have some delay, and
5 we didn't get a specific, but perhaps it be just
6 communicated that it should be flexible?
7 DR. EWENSTEIN: Well, if we need to come up
8 with an amendment for today, I would make it 18 months
9 instead of 6 months.
10 CHAIRMAN BOLTON: Implemented within 18
11 months. So let's start with that one first. All of
12 those who are in favor of altering Item 5 in Option 3
13 to read to implement deferrals within 18 months of
14 final FDA guidance, would their raise their hand?
15 (A show of hands.)
16 CHAIRMAN BOLTON: Okay. Let me read again.
17 The current Option 3, the FDA proposal reads, "To
18 implement the deferrals within 6 months of final FDA
19 guidance." Dr. Ewenstein has suggested that we change
20 that to read, "Implement deferrals within 18 months of
21 final FDA guidance."
22 That is that it would give the blood centers
23 an extra year to adjust to this policy. So that it
24 would not occur within six months of the guidance, but
25 would occur and be implemented within 18 months of the

1 guidance."

2 DR. LURIE: Just making a point that the

3 guidance is probably a year away probably.

4 CHAIRMAN BOLTON: Right. The guidance may

5 be a year away from coming out anyway.

6 DR. PRUSINER: Are we talking about duration

7 of residence, or --

8 CHAIRMAN BOLTON: No, we are talking about

9 implementation.

10 DR. BURKE: I find it difficult to vote on

11 how long we are going to wait until we implement a

12 policy if I don't know what policy it is that we are

13 going to implement. So I think we have the cart a

14 little before the horse on this one.

15 CHAIRMAN BOLTON: Well, it is all sort of a

16 package.

17 DR. BURKE: Okay.

18 DR. NELSON: And the other point about

19 delaying implementation is that this committee meets

20 periodically and revises the guidelines. So if we

21 don't want something implemented for 18 months, we

22 could vote on the policy six months from now, or 12

23 months from now when it is perhaps more clear on what

24 we need to do and when.

25 So although I appreciate the fact that you

1 need to know what is coming down the road, but to me
2 it is not --
3 DR. BURKE: I'm not asking for a vote at
4 this point. It is just that I think it needs to be
5 voted on at the appropriate time.
6 DR. EWENSTEIN: And if I could just respond
7 to that. I think there is a big difference between
8 waiting a year to vote on something that has a six
9 month implementation, and voting on something now that
10 has an 18 month implementation.
11 And I do take the point that one has to know
12 what the whole package is, but what I am trying to
13 respond to is the fact that once we set a policy, and
14 recognizing that it could change again, but once we
15 set a policy, this will give folks more time to
16 respond to that policy.
17 If we spring it on them with only six months
18 notice, it may be harder for them to respond to that
19 policy.
20 DR. EPSTEIN: Yes. I just want to comment
21 on -- and this comes back to a point that Dr. Lurie
22 made very early in the meeting today. We will most
23 likely first issue recommendations as a draft
24 guidance, and then have a comment period, and then
25 review comments.

1 And then issue a final guidance for
2 implementation. So if we say we would recommend
3 implementation within six months of final guidance, in
4 all likelihood we are talking about a year from now.
5 So it could be 9 months to a year. It just
6 depends on how quickly we can move this process alone.
7 So I just mention that to you so that you are aware
8 that if you say you recommend that FDA should advise
9 implementation within 18 months of final guidance, you
10 have to add the time it may take to get us to final
11 guidance, and as to when this might be a policy in
12 effect.
13 CHAIRMAN BOLTON: Dr. Katz.
14 DR. KATZ: There is a practical matter here,
15 and I don't know exactly how to get to the kernel of
16 it. But I think we have heard from the Red Cross, and
17 this is likely a done deal in September.
18 And the independence floating around out
19 there, each of us smaller or larger operations than
20 the other, will have enormous pressures in a policy
21 vacuum that was going to go on for 18 months or so.
22 I don't know that this committee saying we
23 will delay it for 18 months makes any difference.
24 Without some pretty clear guidance from FDA in the
25 short run, we are stuck with half the blood supply

1 doing this, and the other half trying to make up their
2 minds.
3 CHAIRMAN BOLTON: So the suggestion is not
4 particularly helpful?
5 DR. KATZ: I don't think it avoids the
6 precipitating problem.
7 CHAIRMAN BOLTON: Shirley.
8 MS. WALKER: I think what we are basically
9 of mind to take on this would be that if wouldn't be
10 all that bad to have a two-tier type of system. The
11 FDA system would be the minimum standard and ARC could
12 be the maximum.
13 This way we have some flexibility and if we
14 err, we err on the norm. That way we have a win-win
15 situation, and nobody loses. The FDA as a minimum
16 standard which everyone could buy off, and we are not
17 playing children with the American Red Cross.
18 And the American Red Cross can do whatever
19 they wish to do and have a larger standard. But that
20 way the blood supply is adequate when we take into
21 consideration all factors.
22 CHAIRMAN BOLTON: Well, let's just find out
23 how people stand on this. So, again, repeating -- and
24 vote your conscience. Would you prefer the 18 month
25 revision, and so those that would prefer that that

1 item be changed to implement deferrals within 18
2 months of final FDA guidance, raise their hand in the
3 affirmative.
4 (A show of hands.)
5 DR. BELAY: David, we still have a problem
6 of which package, which option.
7 CHAIRMAN BOLTON: Any package. This is not
8 a formal vote. This is a straw poll. So I don't see
9 an overwhelming response. Should I ask for those who
10 prefer that we implement deferrals within 6 months as
11 it reads now for the final FDA guidance? Please raise
12 your hand.
13 (A show of hands.)
14 DR. BELAY: You have six months?
15 CHAIRMAN BOLTON: Six months.
16 DR. FREAS: So, 12 yeses.
17 CHAIRMAN BOLTON: Well, the bottom line here
18 is that except for the question of all of Europe
19 versus part of Europe, we seem to find the FDA's
20 option three proposal as satisfactory. So perhaps
21 what we --
22 DR. EWENSTEIN: David, can I just add one
23 other possible amendment, which was actually the
24 language that was used in the advantages to Option 3,
25 but never made it up to the bullet point.

1 And that was that if you look at Advantage
2 Number 3, that the impact on the blood availability is
3 unknown, but it is estimated to be controllable by
4 instituting both the National Recruitment Campaign and
5 a system to monitor adequate blood supply.
6 And I would like to see the National
7 Recruitment Campaign and a system to monitor the
8 adequate blood supply built into the proposal, and not
9 just stated as an advantage when it isn't part of the
10 package that we are voting on.
11 And I think that if we listen to many of the
12 concerns of the folks who supply these blood products,
13 that is what we heard, and that was that there was a
14 need for a government-blood industry partnership to
15 carry out both the National Recruitment Campaign and
16 the monitoring campaign.
17 CHAIRMAN BOLTON: Okay. Well, I think the
18 only way really to handle that then would be to
19 entertain a motion to modify Option 3 to include that
20 as part of the recommendation. Otherwise, this is
21 going to get too complicated.
22 DR. EWENSTEIN: Sorry. Well, that is what
23 I was proposing as an amendment, that that be included
24 as part of the proposal that we are voting on.
25 CHAIRMAN BOLTON: This is getting impossibly

1 complicated. The motion has been seconded. Do I hear
2 any discussion?
3 DR. BELAY: I think we should come back to
4 that issue after we vote on each option, because if
5 this option is not selected, basically it could become
6 moot.
7 CHAIRMAN BOLTON: Well, this is the first
8 option that we will be voting on, and so the question
9 is whether we should modify it to include as a
10 recommendation that a national recruitment campaign,
11 and a system to monitor adequate blood supply, be part
12 of the recommendation. Further discussion?
13 DR. DE ARMOND: I think it is a great idea.
14 We don't have data on anything. We need data. It has
15 to be part of it.
16 CHAIRMAN BOLTON: Okay. The motion has been
17 made and seconded to add as a recommendation that a
18 national recruitment campaign, and a system to monitor
19 adequate blood supply be added to Option 3. All those
20 in favor?
21 (A show of hands.)
22 DR. FREAS: Fifteen yes votes.
23 CHAIRMAN BOLTON: No votes, please raise
24 your hand.
25 DR. BURKE: I vote for data.

1 CHAIRMAN BOLTON: I'm sorry, but you vote
2 for data only?
3 DR. BURKE: Yes.
4 CHAIRMAN BOLTON: Well, that's not an
5 option. You vote for the amendment or not. No votes?
6 Abstentions?
7 (A show of hands.)
8 CHAIRMAN BOLTON: Okay. That carries. So,
9 now we have that amendment, and the question that I
10 would like to put before you informally is that Item
11 1 under Option 3 is to defer donors for cumulative
12 travel for residents of 5 years or more in any
13 European country, except the U.K., from 1980 to the
14 present.
15 It has been suggested that we alter that to
16 include only part of Europe, or something. I am not
17 sure. For example, France alone. Is it the desire of
18 the committee to vote on this issue as it is written,
19 and as we have amended it, or would you prefer to
20 entertain a motion to alter that first item in any
21 way? Discussion. Stan.
22 DR. PRUSINER: I mean, if you do some very
23 simple-minded math, and say that the risk of variant
24 CJD in France right now is 5 percent of what it is in
25 the U.K., and now you say that France either has

1 porous borders and all of Europe is the same, or
2 France is different.
3 That is a separate issue. But the 5 percent
4 number, if you now multiply 5 years times 12 months,
5 that is 60 months, and 3 months, which we all think is
6 appropriate now for the U.K., is 5 percent of 60
7 months, I think the numbers are approximately right.
8 That is what I am trying to say to you.
9 I am trying to say that 5 years is not an
10 unreasonable number relative to the 3 month number for
11 the U.K. that people seem to want to adopt. So then
12 it seems to me that it is a geographical issue after
13 that.
14 That five years is an okay number relative
15 to variant CJD cases in the U.K., versus the number
16 outside the U.K. And I don't know the right answers
17 to whether it is France, the countries that border on
18 France, that it is all European countries. I just
19 don't know the answer.
20 CHAIRMAN BOLTON: Well, let me give you my
21 concerns here, and that is that -- and I believe you
22 are right, Stan. It is primarily a geographic issue,
23 and if it France alone, Euro-blood is still in the
24 picture for the New York-New Jersey Metropolitan area.
25 If it is all of Europe, then Euro-blood is

1 out, and I think that has a significant impact on the
2 blood supply in the northeast. And for me that is the
3 primary concern. It is a weighing of a marginal
4 increase in safety by adding all of Europe in addition
5 to France, versus a real impact on the blood supply.
6 And as it has been stated here several
7 times, we will revisit this issue in six months or in
8 a year, and as things change, we may adjust this
9 policy.
10 DR. NELSON: Why don't we vote on three
11 proposals then; with France as one, and all of Europe
12 for 5 years as another; and all of Europe for 6 months
13 as a third, which is the Red Cross. And we could on
14 each one of those separately yes or no. Does that --
15 DR. LURIE: I agree that the situation in
16 New York is definitely a particular problem, but what
17 I did see though is that the representative from New
18 York indicated that by 2004 or '05, and I can't
19 remember which, they are planning on not using Euro-
20 blood anyway.
21 So it strikes me that a reasonable approach
22 actually to draw a little bit form what was said
23 before, that to have a specific phase-in just for the
24 Euro-blood probably by 2003.
25 And then leave it, and then that takes care

1 of your concern about the northeast, and then we can
2 vote for all of Europe if you choose to.
3 DR. CLIVER: What I am not hearing said in
4 this is that we are setting it not as the steps
5 between the advent of BSE in a country, and the risk
6 to the consumer.
7 When we voted a little while ago to move
8 form 1996 to the present in the U.K., we essentially
9 said -- and had not said before, that those measures
10 about food supply in England were well taken, and were
11 probably effective.
12 Suddenly, forget it. They have got BSE and
13 we see that they have got VCJD, and surprise,
14 surprise. But, okay, so nothing that they have done
15 since 1996 is regarded as effective.
16 I personally think that now that most of
17 continental Europe is aboard with the same kinds of
18 precautions, as far as the human food supply is
19 concerned, it isn't that relevant whether this country
20 or that has some BSE in it.
21 I think we are doing a pretty good job
22 keeping people from getting it via the food supply,
23 and from that standpoint the fact that we already know
24 that we have got a BSE that led to a VCJD problem in
25 France, I think that is compelling.

1 But I don't think it is a necessary
2 concomitant that every place where there is BSE that
3 the consumer is equally at risk of VCJD. I think we
4 ought to pay attention to the fact that there are
5 these food precautions.
6 DR. BAILAR: If I understand this, I don't
7 entirely agree. I think there is a substantial
8 difference between primary infection from the food
9 supply, and the secondary infections from blood
10 products for which I would expect a long and sort of
11 delayed or smeared out period.
12 CHAIRMAN BOLTON: Where are the donors --
13 DR. BAILAR: I am thinking about the donors
14 who are already infected, but are not apparently ill
15 yet, and this may take a long time to resolve itself.
16 CHAIRMAN BOLTON: Stan, and then Dr. Burke.
17 DR. PRUSINER: I would like to respectfully
18 disagree. I don't know that we know about the safety
19 of the food supply. There have been very few
20 measurements that I believe, and the reason that I say
21 that is that the assays showing me that non-CNS
22 tissues are virtually devoid of prions have been done
23 in in-bred mice, called R3 mice for the most part, and
24 some other mice.
25 And it is now very clear that those mice

1 have titers which are 10,000 fold lower than
2 transgenic mice, that carry a bovine PrP gene. And
3 none of these studies have been done on these
4 transgenic mice.
5 So I just don't think that we know the
6 answer, and really a lot of this work has come from
7 applying work that was done earlier by Bill Hadlow 20
8 years ago in sheep, and there again the mice assays
9 were inadequate to tell us what the real titers are in
10 these other tissues.
11 And so I just don't know the answer, and I
12 don't think anybody knows the answer. So I think that
13 they are real assumptions to which I have difficulty
14 buying.
15 CHAIRMAN BOLTON: Don.
16 DR. BURKE: After Dr. Donnelly's
17 presentation, I asked her specifically whether or not
18 on why she had just used the animals and not factor in
19 the feed control, the food control of the human food
20 chain in her models.
21 And her answer to me -- and I will let her
22 answer again -- is that it is very spotty across
23 Europe, the application of the control of the
24 ingestion of animals older than 30 months, and the use
25 of mechanically recovered meat, and it varied

1 substantially from country to country.

2 And so that we can't use that right now as

3 a factor in our decisions, or at least that is my

4 understanding. Did I restate that correctly?

5 DR. DONNELLY: Yes. Yes, that is what I

6 said, in terms of looking at that, it is very

7 difficult to estimate, especially when you are looking

8 at risk to humans, and what sort of production you get

9 with these various restrictions on particular tissues.

10 And we know that those regulations change

11 when additional data becomes available. But what I

12 would like to point out is that the one thing which I

13 think is very heavily police, and very important in

14 protecting people from infection from the consumption

15 of beef in Britain is this over 30 month rule.

16 That is very tightly controlled. There is

17 a cattle passport scheme which is that you can no

18 longer have passports falling off of ears and things,

19 and it is very tightly policed. It is very heavily

20 patrolled.

21 And the recent intense, sort of inspection

22 of cattle with foot-and-mouth has shown that there

23 wasn't a problem with that. That said, I think if you

24 are comparing risk to people who have been in Britain

25 for six months or more between '96 and 2000, which is

1 -- well, if you are comparing that to Britain and
2 other non-British countries that don't have an over 30
3 month rule, as I have shown you data for France and
4 Ireland in particular, they had higher risks if you
5 are just looking at that time period.
6 So if you are actually going to compare
7 Britain in '96 to -- or '97 to 2000 to other
8 countries, you really are dealing with a very small,
9 and very little evidence of infection in Britain
10 compared to the other countries, because they have
11 these animals over 30 months. So it is a very
12 difficult balance.
13 DR. FERGUSON: Can I just add something? I
14 would like to just kind of second what Dr. Donnelly
15 just said. I mean, that is what we have found out
16 through essentially investigations on the animal
17 health side, is that there is a big difference in --
18 well, first of all, when some of those measures were
19 implemented in European countries, and then also when
20 they were realistically implemented.
21 And when were they put on paper and when
22 were they actually put into effect. So definitely it
23 is a bit spotty across Europe. But I would like to
24 perhaps build a bit on what Dr. Lurie said, and also
25 a suggestion that you had made about separating out

1 France, and that that would address the Euro-blood
2 situation.
3 I have some concern with what kind of
4 drawing that arbitrary line is mostly based on, and
5 the benefits of the Euro-blood outweighing that risk.
6 I think that is completely an arbitrary distinction.
7 And if we are saying we really need the Euro-blood,
8 then let's just phrase it that way.
9 But I think realistically what we are
10 looking at is that the FDA has to go through a
11 noticing and commenting policy on a guidance, and if
12 we make a decision today to recommend a differential,
13 then they go through that.
14 We are talking 9 months to a year, and then
15 we are talking an additional 6 months. Okay. We are
16 in the middle of 2001 and that already puts us at the
17 end of 2003, which is when this is being phased out
18 anyway. So I am not sure how much we need to factor
19 all of that in.
20 DR. LURIE: Well, it would be a pity -- and
21 just to follow up on that, but it would be a pity if
22 we actually thought that there should not be a line
23 drawn in France to draw the line on the basis of a
24 distinction that will end up being irrelevant, and
25 then we would have lost our opportunity to extend it

1 if that is what you wish.

2 CHAIRMAN BOLTON: Jay.

3 DR. EPSTEIN: Just a comment for Dr.
4 Ferguson. Whatever we decide to do here will be on a
5 very fast track. So, I don't think we should project
6 that there won't be guidance in place until 2003. We
7 hope to be able to move quicker than that.

8 But I think the essential question really is
9 can we draw a line somewhere in Europe and part of the
10 dilemma is that the committee in January advised the
11 FDA against a 10 year deferral for all of Europe, and
12 that was non-U.K. Europe.

13 But on the other hand, when the committee
14 voted in favor of a deferral for 10 years exposure in
15 France, which was clearly linked to U.K. beef
16 consumption, the committee felt compelled to further
17 recommend that we do likewise for Portugal and the
18 Republic of Ireland.

19 The problem with that recommendation is that
20 it said to the FDA that the committee was indeed
21 concerned that we should do something about the
22 "indigenous" BSE now recognized and emerging in
23 Europe, and the dilemma is where do we draw the line
24 on indigenous BSE.

25 Should we have a deferral for Portugal, but

1 not for Spain, for example? Should there be deferrals
2 for other countries that have had a large number of
3 cases prior to their food chain controls? For
4 example, Switzerland?
5 So the committee itself gave us a mixed
6 message, and that was part of the FDA's problem in
7 going forward. We thought that we had made the matter
8 simple by saying, okay, there is France, and let's
9 have a vote on France.
10 And then there is Europe, and let's have a
11 vote on BSE in Europe. But what we got was a mixed
12 message that said, yes, France, but no, you can't
13 ignore BSE elsewhere in Europe.
14 But then the question came back to the FDA,
15 well, where do we draw the line, and what is the
16 underlying principle. You see, that is the difficult
17 part, because we don't want to draw an arbitrary line.
18 We want to have a line drawn on the basis of some
19 concept.
20 You know, what concept is it. Is it the
21 concept of BSE incidents, or prevalence per million
22 head? Is it just the absolute number? Is it the
23 absolute numer with and without evidence of food chain
24 control?
25 Does the date of food chain control matter?

1 So, you see, we have sort of moved from having a yes-
2 no on should we be there at that point in time,
3 January 2001, addressing BSE indigenous in Europe
4 through an appropriate donor deferral or not, and back
5 to the question of how can we stratify.
6 And the problem that the FDA has come to is
7 that we see no clear pathway towards stratifying in
8 Europe unless a principle gets articulated that tells
9 us how we ought to do it.
10 And so I think that if the committee wants
11 to turn around and once again recommend some
12 stratified scheme, that it falls to the committee to
13 state what the principle is, because otherwise we
14 won't know whether another country meets that standard
15 or doesn't meet that standard 3 months from now or 6
16 months from now.
17 CHAIRMAN BOLTON: Dr. Davey and then Dr.
18 Burke.
19 DR. DAVEY: I think that what Jerry says is
20 right on it. It is very difficult when we embark on
21 a slippery slope that we have perhaps as a committee
22 embarked on trying to identify and focus on specific
23 countries, or specific percentages of infected beef,
24 et cetera, because that is a slippery slope that is
25 going to continue.

1 And that's because eventually we are going
2 to have to ask about Eastern Europe, and eventually
3 about Asia, and eventually about Africa. And then
4 perhaps about brain consumption in the U.S. which Alan
5 mentioned.
6 It is a slippery slope that we have to
7 embark on with a great deal of preparation. It is
8 difficult to draw a line, a line in the sand, and we
9 don't have the data to do so.
10 So I think we can identify certainly the
11 U.K., and perhaps France, and when we look at France,
12 it is a country which by far had the greatest
13 importation of British beef, beef that was consumed by
14 the French.
15 And this probably in all likelihood led to
16 those three cases and perhaps a few more. However, I
17 have been reassured by some of the measures that have
18 been taken in other European countries, and while we
19 have to make a tough decision, I think we can draw the
20 line with U.K. and France.
21 And to balance that again -- if we extend it
22 to all of Europe, again, the real, the known, and the
23 very dramatic damage to the U.S. blood supply. I
24 think we have to remember what the people said at that
25 podium this afternoon. This is a serious problem.

1 We have an opportunity to make some prudent
2 precautionary measures and not damage the blood
3 supply. So I would again recommend drawing a line
4 around the U.K. and probably France, with 3 months for
5 the U.K. for transfusion deferral, and that makes
6 sense.

7 CHAIRMAN BOLTON: Don.

8 DR. BURKE: Earlier today, you made a
9 proposal that I thought was quite sensible that we
10 haven't discussed, and that was using the criteria of
11 clinical cases of human variant CJD as the criteria on
12 which to define the geography for exclusion from the
13 donor pool.

14 I right now wouldn't know where to begin
15 when it comes to the prevalences in the testing, and
16 the testing is going to be increasing, and probably
17 have better specificity and sensitivity.

18 The clinical cases of BSE, and the country-
19 to-country varying policies of food chain protection,
20 all of which are going to in influence the human risk,
21 and make it virtually impossible to have a sensible
22 internally consistent and logical set of principles on
23 which to make these decisions.

24 And I think that your proposal earlier today
25 made eminent sense to me.

1 CHAIRMAN BOLTON: Well, I appreciate that.
2 Is there any additional discussion on that point?
3 DR. SCHOENBURGER: I just wanted to remind
4 the committee that when I was on it before that one of
5 the underlying principles that several of us used was
6 not so much trying to draw the line about the risks of
7 BSE by various countries, but more what the risk on
8 the supply side would be.
9 One of the reasons for the six months that
10 people have asked me, versus three months, or any
11 visit to England for a criteria for selecting out
12 donors, was a look at the curve of the impact on that
13 particular decision on the supply issue.
14 And the reason for that is that we were not
15 sure, and it is not clear to me that we are still sure
16 today, that the risk that we are talking about is any
17 greater than the risk that we experience in this
18 country with regard to classic CJD and its ability to
19 transmit through transfusion medicine.
20 We are concerned because of many of the
21 things that Stan and others have pointed out, such as
22 the peripheral increase in titers in the spleen, and
23 in the tonsils, and so on, which are worrisome.
24 And that's why we go ahead and put in the
25 restrictions, but still it is a theoretical risk, and

1 the fundamental question in making these hard
2 decisions was not trying to carefully draw a line
3 between England, which we didn't think has much of a
4 risk in Europe, and Germany.
5 But rather which countries can we eliminate
6 that would not create a shortage problem in the United
7 States.
8 CHAIRMAN BOLTON: Stan, and then I am going
9 to move on.
10 DR. PRUSINER: I guess my feeling is that we
11 are getting caught in the middle of specific blood
12 supply issues in the New York area, and this concerns
13 me, and that we are not being able to enunciate to Jay
14 Epstein and others of the FDA of real general
15 principles.
16 And my own personal view as a physician, and
17 taking care of people; whereas, someone who
18 unfortunately might be in an auto accident and need
19 blood in the New York area, I would hope that it
20 wasn't Euro-blood.
21 And I would hope that this could get phrased
22 out, and then in some way I -- you know, I am not sure
23 that I believe these graphs. They are all just future
24 projections, with a lot of points on them that aren't
25 real.

1 So in some way I think we need to be a
2 little careful of this, and I am not sure how to do
3 it, and I am not sure how to think about this, but I
4 personally think there ought to be some way to get rid
5 of this without jeopardizing the blood supply of the
6 country.
7 And there ought to be some directive, some
8 recommendation from this committee, to tell the FDA to
9 figure out how to get rid of it over some period of
10 time. So I have put in my two cents.
11 CHAIRMAN BOLTON: Okay. Well, I think at
12 this point that I would like to entertain any motions
13 that would be made. We have at this point Option 3
14 essentially as it stands, with the amendment to add
15 the recommendation for a national recruitment campaign
16 and a system to monitor adequate blood supply.
17 And I would at this point entertain any
18 motions to modify the first item, which is the
19 question of time of deferral or time of residence, to
20 in Europe, or part of Europe, or any other
21 modification. If there are no modifications, then I
22 think we should go ahead and vote on it.
23 DR. LURIE: Why don't we just vote on it,
24 and if it turns out that people don't want it, then we
25 can decide if you want to go more restrictive or less

1 restrictive.

2 DR. PRUSINER: I was going to suggest that

3 we make one modification.

4 CHAIRMAN BOLTON: And that would be?

5 DR. PRUSINER: And that would be that we

6 would have a clause that would direct the FDA to

7 specifically deal with the Euro-blood problem in a way

8 that doesn't jeopardize the national blood supply.

9 DR. NELSON: I would make one modification,

10 and which we would vote on separately, and that would

11 be that countries in which there were variant CJD in

12 humans would be residents in those countries would be

13 excluded from, and so that would be an exclusion

14 criteria.

15 And that gives some logic at least to what

16 we did previously, which was that we recommended

17 Ireland and France. And if we found one in the Czech

18 Republic, then it would be --

19 DR. PRUSINER: That is a terrible idea,

20 because what that will do is push it all underground.

21 DR. NELSON: Thank you.

22 DR. PRUSINER: This has been the whole

23 problem in the AIDS world, and I think that is the way

24 to have a country -- well, I think that is to

25 punishment a neurologist with death if they ever

1 reported a new variant CJD case.

2 DR. CLIVER: Well, the other thing that goes

3 with that is that we have a case now, and I think it

4 is probably authentic, in Hong Kong, and it certainly

5 was not contracted in Hong Kong.

6 So the mere fact that she was diagnosed in

7 Hong Kong would put the onus on Hong Kong

8 unnecessarily.

9 DR. PRUSINER: Well, the onus on China.

10 DR. NELSON: Okay. But Hong Kong is China.

11 DR. CLIVER: Okay. But not everybody in

12 China had equal access to the U.K. during the period

13 when she was there and apparently got infected. So we

14 are in the situation where a fortuitous diagnosis in

15 some place should not be held against the whole

16 population of that country.

17 CHAIRMAN BOLTON: Well, clearly that is sort

18 of a criterion that would have to include some

19 statement about someone not having previously resided

20 or traveled a certain amount of months in a country

21 that already has had a new variant CJD case. And it

22 begins to get extremely complicated, and I agree.

23 DR. SCHOENBURGER: Just a point of

24 information. That is a case that was clinically

25 compatible in a pulmonary sign by MRI and has a tonsil

1 biopsy that shows the evidence for the new variant
2 CJD.
3 CHAIRMAN BOLTON: And this individual did
4 reside in the U.K. for a period of time?
5 DR. SCHOENBURGER: They did reside in the
6 U.K. for over 5 years.
7 DR. FREAS: For the record, that is Dr.
8 Schoenburger from CDC.
9 CHAIRMAN BOLTON: Okay. Well, I think I am
10 going to take up Peter's suggestion, and we will take
11 a formal vote on Option 3 as it stands, and I will
12 read these individually, plus the amendment that was
13 approved.
14 So, Option 3 is to defer donors for
15 cumulative travel or residence of 5 years or more in
16 any European country, except the U.K., from 1980 to
17 the present. To defer donors who spent any cumulative
18 period of 3 months or more in the U.K. from 1980
19 through the end of 1996.
20 To defer donors who spent more than 6 months
21 on a European Department of Defense base from 1980
22 through the end of 1996 or 1980 through 1990, if all
23 exposure after 1990 was on Department of Defense bases
24 north of the Alps.
25 And to defer any recipient of a blood

1 transfusion in the U.K. from 1980 to the present, and
2 to implement deferrals within 6 months of final FDA
3 guidance.

4 And to institute both a national recruitment
5 campaign and a system to monitor adequate blood
6 supply. That is the question.

7 DR. DAVEY: David, I thought we were just
8 going to vote -- I mean,w e are just going to vote on
9 the European -- on the extent of the European deferral
10 at this point. Am I wrong?

11 CHAIRMAN BOLTON: No, I think -- I've made
12 a Chairman's decision. So go ahead and vote on this,
13 and I will explain that is the question before us. If
14 you believe that the first item, the 5 years or more
15 in any European country, except the U.K., is not what
16 you would like to see, then please vote no.

17 If that is acceptable and all the other
18 components are acceptable, please vote yes. If this
19 is voted down, we will begin entertaining this or
20 another modified proposal. So this is the FDA's
21 Option Number 3 proposal, with the added amendment of
22 a national recruitment campaign, and a system to
23 monitor adequate blood supply.

24 Bill, would you prefer a voice vote or a
25 name vote, or by a show of hands?

1 DR. FREAS: We will do a show of hands, and
2 then whatever is the minority, I will call out the
3 names.
4 CHAIRMAN BOLTON: Okay. All those in favor
5 of the question, please raise their hands and signify
6 aye.
7 (A show of hands.)
8 DR. FREAS: Ten votes in favor.
9 CHAIRMAN BOLTON: All those opposed please
10 raise their hands signifying no.
11 (A show of hands.)
12 DR. FREAS: The opposed are Dr. Burke, Dr.
13 Williams, Dr. Cliver, Dr. Priola, Dr. Bolton, and Dr.
14 Belay, and Dr. McCurdy.
15 CHAIRMAN BOLTON: So what is the tally on
16 that?
17 DR. FREAS: That should be seven opposed and
18 ten in favor. There were no abstentions?
19 CHAIRMAN BOLTON: Oh, I didn't ask for that.
20 Abstentions? No abstentions. So we are through with
21 that question. The motion carries, and so that
22 precludes needing to vote on Items 2, 3, or 4.
23 I am not sure if the FDA needs any -- yes,
24 Bruce?
25 DR. EWENSTEIN: I just wanted to say, and

1 this is after the vote, but I think what Dr. Prusiner
2 said before, and I think what several of us have been
3 concerned about probably should go into the record.
4 And that is that some policy, and
5 independent of Option 3 now, should be put in place to
6 deal with the Euro-blood situation, because I think
7 that is exceptional and needs to be addressed by one
8 means or another on whether it is a deferral of the
9 time line for implementation of Option 3, or some
10 other approach. It needs to be addressed.
11 CHAIRMAN BOLTON: Would someone like to put
12 that in the form of a motion? Is that appropriate?
13 DR. EWENSTEIN: Well, I would suggest that
14 as a motion.
15 CHAIRMAN BOLTON: Okay. Let me see if I can
16 paraphrase it. It has been moved -- or do we have a
17 second on this, or should I -- well, Stan seconds it.
18 Can I paraphrase this?
19 That we are recommending to the FDA that
20 they determine a method of dealing with the or
21 compensating for the loss of Euro-blood in a way that
22 will not jeopardize the national blood supply. Is
23 that an adequate statement of the question?
24 Discussion?
25 DR. BURKE: It doesn't make any sense at

1 all.

2 CHAIRMAN BOLTON: Well, have I done a good

3 job?

4 DR. BURKE: We ought to at least provide

5 some concrete suggestions about what that is other

6 than to say that our vote just created a terrible

7 problem and that somebody else needs to fix it.

8 DR. EWENSTEIN: Well, I had suggested one

9 approach, which was with respect to Euro-blood now, to

10 have a delay in the implementation of Option 3 that we

11 just approved. That is one approach that comes to

12 mind. I mean, there may be others.

13 DR. PRUSINER: Okay. I have an approach.

14 CHAIRMAN BOLTON: Stan.

15 DR. PRUSINER: That the FDA create some time

16 line with decreasing amounts of Euro-blood in

17 consultation with the New York City area blood banks.

18 CHAIRMAN BOLTON: But I think the critical

19 question is where is the extra blood going to come

20 from,and I don't --

21 DR. PRUSINER: Well, that's their problem.

22 CHAIRMAN BOLTON: That's their problem?

23 DR. NELSON: We could since there are

24 several components to this, to the FDA recommendation,

25 or in other words, with regard to the U.K. residence,

1 et cetera, we could delay the implementation of that
2 one -- the Euro-blood issue beyond which the other
3 components, and --
4 DR. PRUSINER: No, no, no. I think there
5 has to be some pressure to get this done, and so there
6 has to be some -- I mean, I don't think we have to
7 have a vote on this. I don't think we have to give
8 the FDA guidance. Jay is a smart man. He will figure
9 it out.
10 (Laughter.)
11 DR. PRUSINER: Karen, will you give him a
12 raise?
13 CHAIRMAN BOLTON: I think that they have
14 heard our concerns about this, and I am sure that they
15 will do something.
16 DR. EPSTEIN: I don't think a vote is needed
17 and I think it is a difficult problem which we will
18 seek to address.
19 CHAIRMAN BOLTON: And likewise I don't buy
20 on this topic, is for us to comment on steps that
21 should be taken to monitor and ensure adequate
22 national and regional blood supplies, et cetera, et
23 cetera.
24 I think we have had adequate discussion on
25 that, and we clearly incorporated a recommendation for

1 that in our vote. So I think we can move on from
2 there. And that, ladies and gentlemen, concludes
3 topic one. We are only about four hours late.
4 The question now is whether we can
5 adequately move on to topic two. Bill, is that --
6 okay. Let's take a 10 minute break, and come back at,
7 let's say, 4:50, and we will begin, I think, with
8 Topic 2.
9 The committee update by Dr. Nightingale is
10 going to be postponed until after Topic 2.
11 (Whereupon, the hearing recessed at 4:38
12 p.m., and was resumed at 4:58 p.m.)
13 CHAIRMAN BOLTON: Can we get the committee
14 members seated, please. We would like to start the
15 second topic of the day, and welcome to the FDA prion
16 marathon.
17 Topic Number 2 is the "Safety of FDA-
18 Regulated Derivatives Prepared in Establishments
19 Proposing to Use on the Same Manufacturing Line,
20 Plasma Which Does and Plasma Which Does Not Comply
21 With Current U.S. Standards, With Regard to Donor
22 Deferral for VCJD Risk Factors."
23 And our first speaker is Dr. Dorothy Scott,
24 and she is going to introduce the topic, and give the
25 committee the charge on the questions. Dr. Scott.

1 DR. SCOTT: Welcome to Topic Number 2 and
2 good evening. Next slide. The FDA is aware that many
3 manufacturers process plasma from both U.S. and
4 European donors in the same facility. The
5 manufacturers were given FDA approval to do this in
6 their license applications.
7 U.S. and European plasma pools of process to
8 separate batches in sequential steps, which are
9 referred to as campaigns. After, for example,
10 European plasma is processed, the equipment is cleaned
11 using cleaning procedures that are FDA approved.
12 And after cleaning, U.S. plasma may be
13 processed using some or all of the same equipment,
14 depending on the manufacturer and the specifics of
15 their license.
16 However, cleaning procedures were approved
17 prior to appreciation of VCJD risk in Europe, and the
18 FDA has not previously formally recommended cleaning
19 or other strategies that would be relevant to variant
20 CJD.
21 So if as a precaution the FDA recommends
22 deferral of blood and plasma donors based on possible
23 BSE exposure in Europe, which appears more than likely
24 at this point, manufacturers that process European
25 plasma will be in the position of manufacturing what

1 is technically referred to as suitable and unsuitable
2 plasma in the same facility.
3 That is, plasma that meets U.S. donor
4 deferral criteria will be manufactured using the same
5 equipment as plasma that does not meet our criteria.
6 As our first question, we are asking the
7 committee to comment on the significance of VCJD risk
8 from campaign manufacturing processes that could
9 result in the potential crossover contamination of
10 U.S. plasma by European plasma.
11 The risk of VCJD transmission by plasma or
12 plasma derivatives is unknown and theoretical as you
13 have heard. However, an experimental model of TSE,
14 such as hamster scrapie, and amounts of active VCJD,
15 low levels of plasma infectivity, and even lower
16 levels of plasma derivative infectivity, have been
17 demonstrated.
18 Specific steps in plasma processing, such as
19 precipitations, chromatography, and depth filtration,
20 for example, can remove prions and infectivity during
21 the preparation of plasma derivatives. Of course,
22 all of this has been done in experimental settings.
23 However, I would like to point out that
24 information is not available about the availability of
25 specific manufacturing steps to inactivate or remove

1 the VCJD agent or the TSE from plasma derivatives,
2 although it is our understanding that the studies are
3 ongoing.
4 I just wanted to make some points about a
5 risk model for the likelihood of VCJD contamination of
6 plasma, and this would by necessity have to
7 incorporate some problematic functions, in terms of
8 our ability to be accurate about them.
9 In particular, the prevalence of VCJD in
10 Europe is unknown, and the infectivity of plasma from
11 a VCJD incubating donor is unknown, and in fact no
12 such infectivity has been documented.
13 The relevance of VCJD to existing studies
14 showing the removal of TSE agents by plasma
15 fractionation is uncertain and debatable at this
16 point. The likelihood of VCJD removal by discreet
17 manufacturers' processes is unknown, although
18 specifics of manufacturing steps based on studies of
19 BSEs may be critical.
20 And finally the likelihood of carryover
21 contamination of VCJD from European to U.S. plasma is
22 uncertain. Since detailed aspects of processing could
23 affect partitioning of TSE agents, the risk
24 assessment, if done, may best be performed in a
25 specific, rather than in a general, fashion.

1 Dr. Baron will be presenting aspects of
2 European donor plasma risk of variant CJD infectivity,
3 and Dr. Davies will present a case study risk
4 assessment for IGIV in the context of facility
5 cleaning. So those two talks will cover aspects of
6 risk assessment, and not to the second question.
7 A second question to the commitment is
8 whether you believe that any additional steps, besides
9 risk assessment, should be taken at this time to
10 address the use of common manufacturing lines for
11 European and U.S. plasma.
12 And the third question should follow, and if
13 so, which of the following steps should the FDA
14 consider at this time. And that should be consider,
15 because we don't want you or ourselves in the absence
16 of certain kinds of detailed information to any one of
17 these particular steps.
18 If indeed additional strategies could be
19 useful, which of the following should we consider.
20 For example, should we consider recommending
21 additional labeling for plasma products made in
22 facilities without dedicated or separate manufacturing
23 lines, which also process European plasma.
24 Now, I will come to each of these, in-turn,
25 and tell you a little bit more about some of the

1 things that need to be thought about. Other means of
2 addressing the issue could include institution of
3 additional facility decontamination cleaning between
4 U.S. and European campaigns, and/or the use of
5 dedicated equipment for U.S. and European plasma.
6 These approaches need not be mutually
7 exclusive. Additional suggestions for FDA
8 consideration from the committee will be appreciated.
9 I will now mention some points about each of
10 these strategies, many of which will be expanded upon
11 by the presenters. The FDA has already recommended
12 general labeling relevant to CJD.
13 In our 1999 guidance, we recommended that
14 all plasma derivatives contain a labeling statement
15 about the theoretical risk of CJD, stated just as CJD
16 overall.
17 The recommended labeling in the warning
18 section states, and I quote, "Because this product is
19 made from human blood, it may carry a risk of
20 transmitting infectious agents, e.g., viruses, and
21 theoretically the CJD agent."
22 New labeling related to processing in
23 facilities which also process European plasma would
24 appear to differentiate products from each other with
25 respect to this theoretical risk.

1 These are some considerations for cleaning
2 and decontamination procedures. First, as Dr. Rohwer
3 will discuss, adequate TSE decontamination in
4 experimental settings is best achieved by combined
5 physical and chemical methods, such as, for example,
6 audoclaving combined with sodium hydroxide.
7 But some equipment may not withstand single
8 or repeated treatments, and for others it may not be
9 technically possible. It would take some amount of
10 time to institute and evaluate new cleaning
11 procedures, as well as cleaning validation methods.
12 Our international colleagues have told us
13 that thorough facility cleaning on a one time basis
14 could take several months, and of note is that unlike
15 the situation for viruses, for TSEs to date there is
16 no validated intentional inactivation or removal
17 procedures during plasma processing, although clearly
18 there are steps in plasma processing which may cause
19 removal.
20 But there have not been steps designed
21 specifically for this. Dr. Davies will be discussing
22 aspects and complexities of facility cleaning. And
23 finally the use of U.S. plasma from dedicated
24 manufacturing lines would seem to in effect eliminate
25 the theoretical risk of VCJD contamination by European

1 plasma.

2 It should be noted that replacement of some
3 equipment could take time, and the time required to
4 install, validate, evaluate, and inspect additional
5 equipment in facilities could have adverse
6 consequences on the supply of plasma derivatives.

7 Dr. Busenbark will present a case study and
8 concerns with institution of dedicated manufacturing
9 lines. And Mr. Healey will address anticipated
10 effects on supply of plasma derivatives in this
11 setting.

12 So thank you for your attention, and if
13 there are any questions, I will take them. Otherwise,
14 we can turn to our first speaker, Dr. Rohwer.

15 CHAIRMAN BOLTON: Are there any questions
16 from the committee members?

17 DR. BELAY: Yes. Dr. Scott, how many
18 manufacturers are we talking about in this category?

19 DR. SCOTT: Virtually all of the major
20 plasma fractionators are involved, without naming
21 names. I believe it is 5 or 6.

22 DR. BELAY: And what percentage of the
23 plasma derivatives will be supplied by manufacturers
24 in the United States roughly?

25 DR. SCOTT: It is not precisely known for

1 the coagulation factors, but Dr. Healey will present
2 an estimate that approximately 50 percent of IGIV will
3 be affected. It is more uncertain so far, and I don't
4 think we have all the data for plasma-derived Factor
5 8, for example.
6 But there will be a variety, and mos
7 products will be affected, and a few of the products
8 might even be relatively unique.
9 DR. BELAY: Will there be a presentation to
10 better define what we mean by European plasma, in
11 terms of where it is coming from, the specific
12 country?
13 DR. SCOTT: Well, by that I mean plasma that
14 is essentially taken from European donors, and used to
15 make products for the European market or other
16 markets. So it may come from anywhere in Europe.
17 Do we have a breakdown of specific countries
18 in all of these facilities that are processing U.S.
19 and European plasma? No, we don't have a list of all
20 the countries for all the products for all the
21 facilities at this point.
22 DR. BELAY: Would that include the United
23 Kingdom, for example?
24 DR. SCOTT: Pardon me?
25 DR. BELAY: Would that include the United

1 Kingdom?

2 CHAIRMAN BOLTON: The U.K.

3 DR. SCOTT: Oh, none of the -- well, the

4 Europeans also have a 6 month U.K. travel deferral,

5 and so that should not include the U.K. plasma.

6 CHAIRMAN BOLTON: Other questions? Okay.

7 We will move to our next speaker, Bob Rohwer, who is

8 going to talk to us about the scientific aspects of

9 decontamination methods for transmissible spongiform

10 encephalopathies. Bob.

11 DR. ROHWER: Thank you, and I am going to

12 talk about some issues which I feel are sensitive to

13 the specific considerations of this particular

14 problem, and that is the effectiveness or lack thereof

15 decontamination of these agents by those methods which

16 are most affected in decontaminating these agents.

17 And their applicability to cleaning and

18 cleaning of surgical instruments, for example. And

19 the points that I am going to make are based on

20 experiments that I did 20 years ago, and it is

21 interesting to me to see that this has become of

22 interest again.

23 I have given this talk several times

24 recently, and so I ask for your forbearance for those

25 of you who have heard this before. I am going to make

1 four main points, and address four main points.

2 One is that the susceptibility to
3 inactivation of TSE agents is actually within the
4 normal range for the more resistant conventional
5 viruses and spores, and that TSE infectivity is,
6 however, nevertheless less resistant to disinfection
7 and/or sterilization.

8 And what I mean by that is that you can kill
9 most of it, but you can't kill all of it. And the way
10 the majority of it behaves is quite conventional, and
11 the way that these resistant sub-populations behave is
12 quite extraordinary in some cases.

13 And that the susceptibility to an activation
14 is an intrinsic property of the agent, and it gives us
15 some idea of what the agent might be, or what its
16 intrinsic properties are; whereas, the resistance to
17 an activation, and this ability to escape total
18 inactivation, is context dependent.

19 It depends on the known year which the
20 infectivity finds itself, and it is therefore a
21 property of the infectivity milieu. These are the
22 publications on which this talk is based, and you can
23 see that they were published some time ago.

24 This is a review that more or less covers
25 the experiments and rationale for them in more

1 discursive fashion, and a more accessible way.

2 Finally, I would like to also direct your

3 attention to this document right here, which was put

4 together by the WHO as part of a panel, which included

5 myself and David Taylor.

6 We put together the inactivation section of

7 this guideline, and we are in concurrence of the

8 recommendations there, and I think that this is

9 actually one of the better extant guidelines for how

10 to deal with infection control of these agents. And

11 a copy of it can be obtained from this site at WHO,

12 this URL.

13 So let me begin by just talking about the

14 process of inactivation so that we are on the same

15 wavelength and so you understand where I am coming

16 from in making the claims that I am going to make for

17 the inactivation process.

18 This is a typical inactivation curve. It

19 could be the inactivation of anything, but viruses,

20 spores, bacteria under some settings, and what have

21 you, and basically the two axis are this.

22 You have your exposure to whatever your dose

23 is down here on this axis, and in this case it is time

24 of exposure to some chemical inactivant, or to a heat

25 treatment, for example, and over here you have your

1 surviving fraction.

2 So up here at 10 to the zero, you have got

3 a hundred percent survival, and at 10 to the minus 1,

4 you have killed 90 percent of the population; and at

5 10 to the minus 2, you have killed 99 percent of the

6 population.

7 And another way of looking at that is by

8 considering it up here, if you had a hundred percent

9 of the population available, and you had a hundred

10 organisms, by the time that you are here, you have got

11 this many left.

12 And by the time that you are here, you are

13 down to only one survivor. There is a lot going on in

14 this very early part of the inactivation process, and

15 in fact chemically and biologically, you talk about

16 the sensitivity of an agent on the basis of its

17 initial rate of inactivation, and it is the

18 extrapolation of that rate back to zero.

19 The other important thing to realize is that

20 down here on this axis, 90 percent of what is going to

21 happen has happened already before we are even at one

22 minute of exposure in this particular case.

23 The next 10 percent is covered before we are

24 even at 99 percent is even before we are at one

25 minute, and at 99.9 percent, we are out here at a

1 little over a minute.

2 And really this part of the inactivation
3 represents only about .01 percent of the infectivity
4 that is actually associated with this material.

5 So this is the extrapolation of the initial
6 rate, and this is telling us how the infectivity is
7 behaving intrinsically, and 99.9 percent of the
8 infectivity.

9 And this is describing how a subpopulation,
10 representing only .01 percent, one part per 10,000 in
11 this case of the population, is behaving.

12 So what does this mean in terms of -- well,
13 how do we interpret this? This susceptibility to
14 inactivation, which is intrinsic to the agent, this is
15 a far less complex part of the inactivation to
16 analyze, and there are far fewer controlling
17 perimeters. They are agent specific.

18 And whereas over here, when we start talking
19 about this region, we have a lot of different
20 parameters that can affect the shape of this curve,
21 and you can get different shapes, depending on how you
22 balance these various factors.

23 And so among those parameters are the
24 container itself, where there are potential
25 sanctuaries where the infectivity can hide. There are

1 cold factors which may be present which may protect or
2 shelter the infectivity from Ph temperature, buffers,
3 reductants, and that type of thing.
4 The actual type of tissue that you start
5 with or the other components of the mixture can affect
6 this. For example, if there are surfactants present,
7 or oils.
8 Whether you mix, actively mix, or you just
9 do a static exposure, and then there are other
10 technical issues which can also affect the outcome of
11 an experiment like this.
12 And this is just to point out that when we
13 talk about the sensitivity to inactivation, we are
14 talking about an inactivation rate constant that is
15 characterized by inactivation rate constant, which is
16 reduction in survival as a function of the interval of
17 dose.
18 And so in this particular family of curves,
19 if we -- this inactivation at this rate, this is
20 showing more susceptibility than curve two, curve
21 three, or curve four.
22 So in comparing agent properties, we are
23 looking at the properties which are intrinsic to the
24 agent, which are reflected in the initial rate of
25 inactivation, and this represents the vast majority of

1 the inactivation that is occurring, and the
2 interpretation is less complex.
3 The side of the residual fraction is a
4 complex function of environmental parameters, and it
5 cannot be used to compare the intrinsic sensitivities
6 of agent strains.
7 Now, I am going to talk about some specific
8 experiments with the TSE agents, and first we will
9 consider chemical inactivation. There are two main
10 chemicals which everyone has agreed on that are
11 effective in killing these agents. One is bleach, and
12 the other one is hydroxide.
13 So in the case of bleach, this is an
14 experiment in which a 10 percent brain homogenate was
15 exposed to bleach at the concentration at which it is
16 recommended to be used for disinfecting diapers, for
17 example, a half-percent.
18 And these are the inactivation kinetics for
19 scrapie, in red, and fora couple of test viruses which
20 were mixed with 10 percent brain homogenate, and
21 inactivated at the same time as this experiment.
22 These are bacteriophages. This is a
23 bacteria stage that is very similar to a parvovirus in
24 structure. And this is our FD, which is a close
25 relative to M-13, the virus we use in the lab for

1 cloning.

2 In the presence of a brain, you can see that

3 the scrapie agent has killed very, very rapidly down

4 to the level of 99.9 percent, killing just upon

5 contact with hypochlorite at this concentration.

6 David Taylor has done experiments at 5

7 percent hypochlorite, which drives this right down to

8 a total killing in a very short time as well. We

9 haven't actually looked at kinetics, but within a 30

10 minute exposure, for example.

11 But what is notable here is that when you

12 put PhiX 174 in brain, or FD in rain, you also get

13 plateaus for these viruses as well. They are at a

14 somewhat lower level, but these are real effects here.

15 This is not an unfamiliar phenomena. It is

16 something that has plagued water purification for

17 years, vaccine production by inactivation of viruses,

18 et cetera, and it depends on the total amount of

19 interacting organics that are present in the mixture

20 that provides some sort of protection or sanctuary to

21 the total inactivation of the virus.

22 Over here we have these same viruses in PBS

23 in a highly purified state, and they are killed very

24 rapidly to the limits of detection. Next slide.

25 And the next example that I am going to give you is

1 sodium hydroxide.

2 This is the inactivant that we are most
3 comfortable with in my laboratory for routine
4 disinfection of these agents, and this is an
5 experiment in which I did with Paul Brown quite a long
6 time ago, in which we looked at a guinea pig model of
7 Creutzfeldt-Jakob disease, and the hamster model of
8 scrapie, at two different time, and at three different
9 concentrations.

10 And what you can see here is that there has
11 been a lot of effect by 15 minutes, and by an hour of
12 exposure at one normal, we have killed to the limit of
13 detection. That means five logs or greater.

14 We couldn't detect more than that, because
15 that is all that we put in, and that is all that we
16 could assay by the time we diluted and assayed. And
17 then in the case of scrapie, we got the same result
18 over here by 60 minutes.

19 Nevertheless, we had quite a high level of
20 effectiveness, even at a tenth normal, and at the same
21 times and concentrations. At .01 normal, a 10-fold
22 dilution of a tenth normal, it is becoming marginal.

23 So somewhere between a tenth normal and one
24 normal, we lose efficacy in this procedure. This is
25 done at room temperature. And by going to one normal,

1 we have given ourselves quite a large margin of safety
2 in using this reagent.
3 These are two other conditions which are
4 similar and fall consistent with this, but let's go
5 on. We don't need to discuss that here. Now, sodium
6 hydroxide has been looked at by lots of other people,
7 and this is a table just summarizing those experiments
8 here.
9 There are a number of different conditions,
10 different times of temperatures listed here, and here
11 are the results, and the things that I want to point
12 out is in yellow here I have highlighted those
13 procedures which gave complete destruction of
14 infectivity to the limits of detection of the assays
15 that were being used.
16 But a lot of people saw survival under some
17 of these conditions, and usually at sort of the limits
18 of detection. So it is not a perfect method, and
19 there are conditions where the infectivity can escape
20 total inactivation by this method.
21 Now, we are going to come back to that in a
22 little bit, but first we are going to talk about heat
23 activation, which shows a very similar pattern. Next
24 slide.
25 This is an experiment looking at 121 degrees

1 centigrade, which was the old standard for autoclave;
2 one atmosphere of pressure, 121 degrees, for some
3 period of time.
4 This is an experiment which was done with
5 highly dispersed brain homogenate in the hamster
6 model. It was prepared by sonication, and it was
7 sealed into ampoules, and these serum bottles were
8 placed in an oil bath so that we could take the
9 samples at very precise times.
10 We had thermistors imbedded in one of these
11 bottles so that we could monitor the temperature, so
12 that we knew exactly how much exposure we were getting
13 at each one of these times.
14 And what this shows us is that the
15 infectivity of the 263 model is highly sensitive to
16 inactivation by 121 degree wet heat. By the time that
17 we got the temperature, and when we took the first
18 sample here, we had already killed 99.9999 percent of
19 the input infectivity.
20 Nevertheless, there is a residual amount of
21 infectivity which took longer at the limits of the
22 assay, and we actually had an animal eventually that
23 came down at 60 minutes, after 60 minutes of exposure,
24 and a long incubation period, one animal in the
25 undiluted material that showed infection out here.

1 Well, let's go on. Well, this is -- there
2 is another way that you can look at these experiments,
3 and David Taylor has done a large number of
4 experiments like this. They are in several
5 publications of his, and in which instead of starting
6 with a highly dispersed brain homogenate, he starts
7 with a macerate.
8 What a macerate is, is a mushed up brain.
9 here is no dilution. There is no buffer added and
10 nothing like that. He mushes up the brain, and puts
11 it in a tube, and then puts it in the autoclave, and
12 actually does the experiment in a real autoclave.
13 Autoclaves under these regimes for this
14 amount of time, there is a lag time for getting to 134
15 degrees, and a lag time for getting down to a
16 temperature at which you can open the door again.
17 And rather than looking at the kinetics, he
18 just looks at the end point of these experiments, and
19 here you get as you would expect, 19 out of 19 animals
20 that did not get the treatment still show infectivity.
21 But even after 134 degrees at 60 minutes, he
22 has got animals surviving this procedure. Now, how do
23 we interpret this kind of data? I think it is
24 important to realize that what we are looking at here
25 are limiting pollution titrations.

1 You are inoculating 22 animals,but only 14
2 animals get sick, which means that you have killed
3 almost everything. You are out at the end, but there
4 is still some infectivity left.
5 And what do we mean by eliminating dilution
6 titration? This is a case where we inoculate a bunch
7 of animals with -- by the intercerebral route the most
8 sensitive method of inoculating an animal for
9 detecting the infectivity.
10 And we can only inoculate a small amount
11 into every animal, but my inoculating 50 microliters
12 into 20 hamsters, for example, you can look at a
13 milliliter of infectivity, of sampling, next.
14 If five of those animals get sick after a
15 year of monitoring, you can say that you had 5 out of
16 20 get sick, and five dead out of a mil of sample that
17 was inoculated, and you have a titer of about one
18 infectious dose per mil.
19 If we analyze the Taylor data in that way,
20 and put it on next, and put it back on this curve, it
21 is indicated in the red right here. So it is not at
22 all inconsistent with this data.
23 In fact, it is quite consistent with it, and
24 it just means that a macerate in this form produces a
25 lot or a significant amount, or rather a small amount

1 of survival out at even these high exposure levels to
2 what heat next.
3 So what is responsible for this. Well,
4 there is several different possibilities. One, there
5 could be interesting differences between this material
6 that is surviving this heat. Maybe it is heritable.
7 This is something that certainly needs more study.
8 But to the extent that it has been looked
9 at, it doesn't look to me like this is the explanation
10 actually. And arguing strongly against it is this
11 context dependency. It depends on what form you put
12 the agent in on how much survival you get.
13 Aggregation could definitely contribute to
14 something like this, but we get a very different
15 kinetic picture if it was aggregates. We should see
16 a plateau at the beginning of the inactivation, and
17 which falls off later as the aggregates are wiped out.
18 And finally that leaves us with
19 compartmentalization, and this is what I favor. My
20 guess is that the inactivant is not actually reaching
21 the infectivity, and you have to open or destroy the
22 compartment in which it is hiding in order to destroy
23 the last little bit.
24 This is easier to understand in the context
25 of sodium hydroxide than it is in the context of steam

1 sterilization, where everything should get hot. But
2 maybe we can explain it. Let's go on.
3 This is just considering this again and
4 let's go on. And let's just compare again the
5 difference between the experiment fit that I was doing
6 and the experiment fit that David was doing.
7 This was highly dispersed material, versus
8 a whole brain,a nd it was sealed in a bottle, and in
9 carefully controlled conditions. It was basically an
10 idealized situation, because I was interested in
11 looking and answering this question of what is the
12 intrinsic sensitivity to heat of these agents.
13 David had a different objective in mind. He
14 wanted to know what is the worst case situation. If
15 we had something like a macerate, a piece of tissue
16 contaminating our process stream, or our flask, or our
17 scissors, how could we really kill it by these
18 methods.
19 And so he is looking at a -- instead of a
20 constant steam, it is static, and it is a worst case
21 situation. Also bearing on this is the sensitivity of
22 these agents to dry heat sterilization.
23 Dry heat is far less effective than wet heat
24 at these temperatures in sterilization. This is an
25 experiment that was done by Paul Brown some time ago,

1 about 10 years ago, looking at dry heat sterilization.
2 And it is not terribly remarkable. I mean,
3 some spores in this range as well, but he gets limited
4 -- there is limited inactivation, starting with 10 to
5 the 9th or so infectious doses in this particular
6 experiment.
7 He is only killing down to a level of 10 to
8 the minus 2 and 10 to the minus 3 after 10 minutes, or
9 60 minutes of exposure to 160 degrees centigrade.
10 Next slide.
11 So what is going on here? Well, it seems to
12 me that what may be happening in these experiments is
13 that at a very low frequency we are actually drying
14 some of the material on the walls of our vessels. It
15 is being protected possibly by brain fat.
16 And fat can produce an anhydrous
17 environment, and when fats are oxidized, they become
18 varnishes. Varnishes are essentially plastics,
19 polymerized fats or plastics.
20 And essentially you put your infectivity in
21 a different type of container than the aqueous
22 environment that you are seeking to test. Next slide,
23 please.
24 And the lesson here is that if the reagent
25 can't reach it under those circumstances, it can't

1 inactivate it. And this is quite plausible it seems
2 to me in the autoclave situation, especially where you
3 ramp up the temperature, you are at temperatures where
4 you are not inactivating.
5 But you may be drying the substance on to a
6 surface, or to the walls of the vessel, and creating
7 a population that can survive the infectivity. Next
8 slide.
9 And what I want to remind you here again by
10 looking at this again is that this is something that
11 can be a problem even if it happens very, very rarely.
12 And what this data is telling us is that
13 this is a very rare occurrence. It is a parts per
14 million occurrence, or parts per 10 million
15 occurrence. It represents a very small part of the
16 population. But it is nevertheless a serious issue
17 for decontamination and sterilization. Next.
18 Again, just to summarize, 132 degrees
19 centigrade is a significantly higher temperature than
20 121 degrees centigrade for a steam sterilization,
21 where the inactivation takes place in minutes.
22 However, for a dry heat sterilization, 132
23 degrees centigrade is only incrementally more
24 effective than 121 degrees centigrade, and where the
25 inactivation could take days at those temperatures for

1 some agents. Next.

2 So, my take home here is that with steam
3 sterilization, these agents are not intrinsically
4 resistant to steam sterilization. The problem is with
5 the delivery of the inactivant. Next.

6 And the same thing could be happening in the
7 case of sodium hydroxide, though it is a little hard
8 to imagine how it is escaping. But I will say this.
9 I do know that if you put the infectivity in a plastic
10 bag and throw it into your one normal sodium
11 hydroxide, you are not going to inactivate anything.

12 And if at the levels of parts per million we
13 have got little plastic bags in there hiding a very
14 small, unrepresented as part of its population from
15 the sodium hydroxide, and that could come in the form
16 of micelles, or something else of this nature, that
17 could account for what we are seeing as the resistant
18 population. Next.

19 So how do we get around this? Well, it is
20 important -- the lesson here is that for effective
21 sterilization by these methods, you want things that
22 are -- you want well dispersed materials, and
23 homogenization can help, and surfactants can help
24 hopefully.

25 You want to eliminate sanctuaries, and you

1 can do that by agitation. You want to keep things wet
2 so that they can't dry out. And my guess is that as
3 you refine materials, you provide less and less
4 opportunities for protective associations.
5 You get rid of the fats, and you get rid of
6 these random associations which may protect, though
7 that is not something that has been studied in a
8 systematic way. Sterilization prevents drying, and
9 that is one of the most important lessons that we have
10 learned from this comparison.
11 And in our laboratory, we make sure that we
12 emersed our things in water prior to steam
13 sterilization, or subsequent to use. We store them in
14 water and then get them in the autoclave, and combine
15 two or more methods, heat and hydroxide.
16 There have been several studies looking at
17 this combination, and this is always been highly
18 effective. Next slide.
19 Now, because of the topic here, there may be
20 special vulnerabilities of instruments to TSE
21 contamination that we should be considering. The
22 buildup of tissue in hinges, joints, knurling, teeth,
23 and other irregular surfaces or pockets.
24 These are things that we should be aware of
25 and should be addressing. The drying of tissue on to

1 instruments and surfaces, and the inaccessibility of
2 mating surfaces. For example, in forceps and
3 scissors.
4 And then imperfect contact with the
5 inactivant once we bring it into contact. If there
6 are bubbles, or residues that are keeping the
7 inactivant from actually reaching the infectivity, we
8 are not going to get an activation. Next.
9 These are the conditions that we use for
10 sterilizing instruments in our laboratory. We wipe
11 them clean between uses if we are doing a series of
12 dissections, for example, and using either PBS or 2
13 Normal sodium hydroxide to keep the tissue load down.
14 If we emersed them under sodium hydroxide
15 for at least an hour, and usually overnight, and then
16 we transfer -- if they are sensitive, we transfer them
17 to water before sterilizing, though we don't let them
18 dry.
19 And if they are not sensitive, we autoclave
20 them in the presence of sodium hydroxide. There are
21 a lot of stainless steels which takes this just fine,
22 and can be treated this way.
23 And then once we are finished with our
24 decontamination step -- and we consider this a
25 decontamination -- that's when we clean the

1 instruments, package them, and sterilize them for use
2 or reuse just as you would normally.
3 Now, the topic here was to consider between
4 batch sterilization and a process environment, and
5 these are the things that come to my mind, in terms of
6 the special vulnerabilities of process equipment.
7 Head spaces where you have got air, and
8 opportunities possibly for drying out potential
9 problems. If you have got places that are
10 inaccessible to the disinfectant, those are the other
11 problems.
12 The modern methods of CIP disinfection
13 really have tried to address this in a very effective
14 way, and I think this is -- that these are remarkable
15 pieces of equipment, and remarkable methods. But
16 whether they are effective for these agents, it is
17 hard to know.
18 Incompatibility with TSE inactivants is
19 another problem. The conditions required for TSE
20 inactivation may require impracticable amounts of
21 time, temperature, and reagent concentration for this
22 use.
23 And what I think is really the biggest
24 problem is the lack of TSE-appropriate assurance
25 methods. You know, how are we going to know whether

1 we have really accomplished this or not even if we
2 think that we have. Next.
3 These are some of the strengths of these
4 methods, and I think that people are going to go over
5 these in great detail in a moment. So I think we can
6 just go on.
7 And finally I just want to emphasize that
8 any method that claims to be able to inactivate TSE
9 agents really has to be validated, because these
10 methods are very sensitive, or can be very sensitive
11 to the details under which they are conducted.
12 And we have had unexpected surprises in the
13 past and we don't really want them in the future. And
14 I just mention this paper right here as a warning in
15 this nature, and that is a paper by -- that came out
16 of the Weissman lab, talking about the infectivity
17 that is associated with stainless steel surfaces.
18 And this is actually quite an alarming
19 report, in which they have shown that by contaminating
20 a stainless steel wire by simply exposing it to brain
21 homogenate, and then extensively washing it with PBS,
22 and then similarly inoculating animals with this wire,
23 they didn't see any reduction in incubation time in
24 these animals through several passages through these
25 animals, or I mean, several passages of this wire

1 through animals.

2 And there has been some more work done on

3 this, though it has not been published, but I was

4 privileged to hear this at a meeting recently. And it

5 seems to be holding up that -- it is actually quite

6 difficult to get this infectivity off this stainless

7 steel surface.

8 This is something that really needs to be

9 looked at much more thoroughly than it has so far to

10 see whether this is a problem or not, and especially

11 if it is a problem in the context of these various

12 strong denaturing agents, sodium hydroxide and other

13 alkaline reagents. Next.

14 Now, this is my own take on this, and I

15 don't know that this will come up, but I have got the

16 lecture at the moment, and so I want to make this

17 point here, and that is when considering the efficacy

18 between batch cleaning and this idea of separate

19 facilities and that type of thing, I think it is

20 important from my perspective, that it seems important

21 at least to consider the fact that geographical

22 deferral does not remove all risk.

23 The best that we are hoping for in the

24 discussions that have taken place today is a removal

25 of 90 percent of the exposure. And moreover there is

1 no recommendation for withdrawal, for lapses in this
2 policy, where mistakes are made.
3 So when we are talking about a cleaning
4 protocol between batch cleaning protocol, I don't
5 think it should be held to a higher standard than the
6 standard that we are actually asking for in our
7 deferral policy.
8 And as an example, you have to consider if
9 we go to the big effort of separating North American
10 plasma from European plasma fractionation, how are we
11 going to handle the fact that there is actually a
12 residual 10 percent risk associated with North
13 American plasma that is irreducible at this time.
14 And what is going to happen when we do see
15 a variant CJD case in North America, and I think that
16 you can argue that given enough time that we are
17 likely to see such a case. Next.
18 Finally, while I am on the soap box here,
19 let me just point out one other point about this
20 analysis, and that is when we consider this survival
21 in response to 1N sodium hydroxide at these very high
22 temperatures in a steam environment, and the things
23 that escape breach, does this really tell us anything
24 about what is causing these diseases, whether it is
25 viruses or prions, as represented by PrPres here.

1 Well, in fact these methods are very, very
2 aggressive methods. They kill viruses as we know
3 them,but they also destroy PrPres as we know them as
4 well.
5 So if you are going to invoke this as
6 evidence for the existence of prions, it is really not
7 very supportive of this model. And if you are going
8 to invoke prions, and if you are going to invoke this
9 as evidence, you have to invoke something else besides
10 PrPres.
11 And the only thing that has been -- I mean,
12 there have been suggestions that things like inorganic
13 ions are responsible for this, and that type of thing.
14 But I don't think it is really taken very seriously.
15 Next.
16 Finally, I think we do need more research in
17 this area. We need to understand the underlying
18 principles of resistance. What I have given you here
19 is really a hypothesis, and not proof.
20 We need to develop a more robust and
21 comprehensive methods for TSE sterilization that are
22 compatible with the materials that we need to
23 sterilize; and we need to establish the
24 vulnerabilities and limitations of existing and future
25 methods.

1 And finally we need to validate existing and
2 future methods. This requires infectivity models
3 because we need to look at infectivity, and this is
4 costly and time consuming, but the sooner we get
5 started the better. Next.
6 This is just again to remind you that this
7 is a good place to go for a general discussion of this
8 topic, and for a much broader discussion of infection
9 control of these agents, and I believe that is the
10 end. That should have been the last slide, and I will
11 finish there.
12 CHAIRMAN BOLTON: Thank you, Bob.
13 Questions?
14 DR. CLIVER: Yes. I followed your argument
15 reasonably well, but one thing I was hoping to hear
16 you mention is in March of last year, Paul
17 Brown and co-workers reported having ashed infectious
18 hamster brain at 600 degrees, and resuspended it with
19 phosphate bumper saline, and have gotten 5 out of 35
20 intracerebral inoculated hamsters develop TSE.
21 And the obvious control of ashing normal
22 hamster brain wasn't done, or at least it wasn't
23 reported, but having said that then, if ashen wasn't
24 obviously exempt from any of the inactivants that
25 would do this, I think it possibly calls in to

1 question the validity of the assay system.

2 DR. ROHWER: It is a validity of the assay

3 system or the validity of the experiment. And I think

4 that is an experiment that definitely needs to be

5 reproduced with controls, and your criticism is well

6 taken.

7 CHAIRMAN BOLTON: Dr. Belay, first, and then

8 Dr. Prusiner.

9 DR. ROHWER: But that was the experiment

10 that gave rise to this speculation; and, well, if it

11 is not protein, then it must be something else,

12 inorganic, that can survive ashing.

13 DR. CLIVER: It could be hamster brain with

14 latent TSE and that relationship.

15 DR. ROHWER: Well, I see. Well, there are -

16 - I don't want to go through a detailed analysis of

17 that experiment, but I will say that I think it merits

18 doing over.

19 DR. BELAY: Bob, I am trying to understand

20 one of your conclusions. I think you said that if you

21 take 10 percent brain homogenate, and then autoclave

22 it at 121 degrees celsius, then you indicate a

23 dramatic decline in the percentage of the concentrate,

24 or there is a decrease in the concentration of the

25 agent.

1 But there was a small group of what you
2 called resistant subpopulation that would remain in
3 the system. And in this so-called resistant
4 subpopulation, it is not intrinsically resistant. It
5 could be -- I think I heard you say it could be that
6 they are probably hiding in some of the tissues, and
7 not necessarily intrinsically resistant.
8 DR. ROHWER: I'm sorry that I didn't get my
9 point across, but what I was trying to point out here
10 is that by comparing the wet heat inactivation and the
11 dry heat inactivation, is that that temperature of 121
12 degrees is a very effective temperature for steam
13 sterilization of these agents.
14 But it is a very ineffective temperature for
15 dry heat sterilization of these agents, and so what I
16 am proposing is that somehow someway that at the level
17 of parts per million in that sample, there was
18 material that only saw a dry heat environment.
19 And one of the ways in which I think that
20 might have happened is if it did dry on the side of
21 the vial in the process of -- well, when you plunge
22 this thing into an oil bath, it boils immediately and
23 throws the liquid into or on to the sides of the vial.
24 And if it flashes off and dries there, with
25 a nice lipid barrier over the top, it may never see

1 steam. That part of the infectivity may actually be
2 exposed only to the dry heat environment, and as a
3 consequence, that's why it survived.
4 DR. BELAY: That's right. So --
5 DR. ROHWER: And that's why it would be a
6 problem for something like head spaces and that type
7 of thing in tanks, where you have an agitator throwing
8 things upon the walls and that type of thing, and you
9 have the opportunity for something like that to
10 happen.
11 DR. BELAY: So one possible intervention
12 could be then to treat the tissues with some kind of
13 chemical that would disintegrate the tissues so that
14 the agents would be exposed to the heat?
15 DR. ROHWER: Well, I think that is -- one of
16 the reasons why a combination of sodium hydroxide and
17 heat is -- well, sodium hydroxide becomes incredibly
18 more aggressive at higher temperatures than it is at
19 room temperature. So that is probably the main
20 reason.
21 But certainly using diagonal methods, and
22 using a chemical method, plus a physical method, is a
23 very smart way of conducting any type of sterilization
24 procedure. And it seems to work in the case of these
25 agents for hydroxide and heat.

1 DR. BELAY: I have reviewed that study that
2 you mentioned from the Weissman group. One of the
3 things that they didn't do was they -- I guess they
4 treated them with PBS and other chemicals, but they
5 did not go ahead and autoclave the instruments and see
6 if there is any infectivity left after the autoclaving
7 process.
8 Now, do you know any group that is doing a
9 similar study to basically replicate the kind of
10 situation that you would see in a hospital situation,
11 where they would treat the instruments, and get rid of
12 the tissues, and wash them away with some kind of
13 chemical, and then subsequently autoclave the
14 instruments and see if there an any infectivity left
15 on the instruments?
16 DR. ROHWER: We have --
17 CHAIRMAN BOLTON: Let me interrupt for a
18 second, Bob. I just wanted to assure everyone that we
19 have been told that this is a false alarm,a nd so
20 there is no fire ongoing. We will not be heat
21 inactivated.
22 (Laughter.)
23 DR. ROHWER: We do this on a routine basis,
24 in the sense that we can't afford to throw our
25 scissors and forceps away at the rate that we use

1 them. So we go through this very extreme
2 sterilization protocol to make sure that we are not
3 transferring infectivity from experiment to another.
4 And I would take as evidence of the efficacy
5 of that that we have done these -- a large number of
6 these blood studies over the last four years, where we
7 have inoculated hundreds of animals, and never
8 infected any of them, and with instruments that were
9 processed in this very way.
10 And these were animals where we were looking
11 for residual infectivity in, say, Fraction 2 or
12 Fraction 5, from a plasma infractionation. So we have
13 that evidence, which is antidotal, and it is not
14 systematic, from our own handling of these utensils,
15 and treating them in this fashion.
16 And which makes me believe that this can
17 work if you do it right. I do know or I have heard at
18 least that there was a major, I believe, EC or else
19 U.K. award, to look at stainless steel of different
20 makes and types, and finishes and that type of thing.
21 And the ability of those surfaces to retain
22 infectivity, and the ability to remove that
23 infectivity by these types of sterilization methods or
24 various types of sterilization methods. But I have no
25 idea where they are in those studies, and I am not

1 actually sure who is doing them.

2 CHAIRMAN BOLTON: Stan.

3 DR. PRUSINER: Just a very quick comment.

4 Coming back to the ashing experiments. The number of

5 animals that became ill after one minute of ashing or

6 three minutes of ashing, I guess it was, in exposure

7 to these extreme temperatures was very, very few.

8 And more animals became ill if the ashing

9 procedure was prolonged to 15 minutes. Now, I just

10 think that this paper should have never gotten

11 published.

12 DR. ROHWER: That data is summarized on that

13 complicated slide that I skipped over, but there were

14 a number of flaws there.

15 CHAIRMAN BOLTON: I think we can feel

16 comfortable, but those data should be reproduced

17 before the committee bases any decision on that level

18 of resistance to inactivation.

19 DR. EWENSTEIN: This may be naive, but at

20 least for coagulation proteins, and getting away from

21 the steel, and to the resins --

22 DR. ROHWER: I am having trouble hearing

23 you.

24 DR. EWENSTEIN: Okay. Sorry. Turning away

25 from the steel and the hardware to the resins that are

1 used for some of the coagulation proteins. As you
2 know, they use monoclonal antibodies in a light of the
3 production, but can you imagine from your own work,
4 and from the reading of the literature, sort of what
5 approaches would be possible that would preserve those
6 resins and still inactivate PrPres?

7 I mean, is that theoretically possible, or do
8 you know if there is data that shows that it is
9 possible?

10 DR. ROHWER: I think you could assure
11 yourself a very nice retirement if you could come up
12 with that solution.

13 DR. EWENSTEIN: That's what I thought.

14 DR. ROHWER: Those biological materials
15 attached to resins like that are a real point of
16 vulnerability in these fractionation systems, and I
17 think the solution is that you have to protect those
18 resins so that they never see that exposure to begin
19 with, or else you have to have something downstream
20 with those resins that is very effective, in terms of
21 removing any residual infectivity which may have come
22 from those chromatography steps.

23 With that said, there are resins, the
24 plastic resins, the plastic ion-exchange resins, which
25 do quite nicely in 1N sodium hydroxide, and it can be

1 regenerated with 1N sodium hydroxide.

2 And they don't have the beautiful ligand
3 specificity of a monoclonal antibody, but they are
4 also used in these processes, and I think they present
5 less of a risk for that reason, provided that they are
6 decontaminated in that way.

7 On the other hand, I haven't seen anybody,
8 and we have not been asked to look at decontamination
9 of a plastic resin with sodium hydroxide just to test
10 how effective it is. I don't know actually.

11 DR. BELAY: Rob, I'm not sure if I made
12 myself clear, but most of my concerns --

13 DR. ROHWER: I'm sorry, but I can't hear
14 you.

15 DR. BELAY: I'm sorry. The primary concern
16 that I have with all this inactivation studies is all
17 this inactivation studies use either grounded up brain
18 tissues, or brain homogenates, and in common sense
19 infection control principles, they tell us that we do
20 not inactivate tissues.

21 We inactivate instruments that potentially
22 came in contact with the tissues, and it would be most
23 appropriate to replicate this kind of studies on the
24 instruments that have been cleaned and properly
25 disinfected, and see if any one of these methodologies

1 that you described would actually work in completely
2 activating the agent.
3 If you just inactivate or try to apply the
4 heat for homogenates or grounded up brain tissues, you
5 would potentially just cook the --
6 DR. ROHWER: I get your point, and it is a
7 valid one, and I think that is why the Weissman
8 Laboratory established this stainless steel wire
9 model.
10 They wanted something that was eminently
11 inoculatable, which they could test, and they were
12 very surprised by this first set of experiments that
13 they did. They are not the only ones that can work
14 with it.
15 They told us how they did it, and it
16 certainly does need to be pursued, just in the way
17 that you suggests here, and it is a nice paradigm I
18 think for looking at exactly that type of question.
19 CHAIRMAN BOLTON: Bob, I thought that there
20 was a published study -- and unfortunately my addled
21 brain cannot think of it now, but where that was done,
22 and where brain tissue was placed on a stainless steel
23 surface, and then washed, and then autoclaved, and
24 then assayed. But I don't recall where that came
25 from.

1 DR. ROHWER: Dr. Asher has done some -- what
2 are called use dilution tests, but I think he used
3 glass, and not stainless steel. But if you would like
4 to say something about that, that might be
5 appropriate, yes.
6 DR. ASHER: We used class because it could
7 be pulverized, and because it was based on a
8 conventional viralcidal (phonetic) model. Some day,
9 if the regulatory load decreases, I will publish that.
10 CHAIRMAN BOLTON: Other questions for Dr.
11 Rohwer?
12 DR. PETTEWAY: Yes, just a comment. I think
13 that this is consistent with what you are saying, Bob,
14 is that we need to be careful about generalizing about
15 stainless steel and prions adhering to stainless
16 steel, and inactivation.
17 That it is likely that where prions go, and
18 whether they are resistant or not, or what they
19 associate with, be a function of independent and
20 individual processes.
21 And the matrix and the materials that those
22 prions associate with, or would associate with, in
23 those processes. So I would just caution against
24 generalizations in this regard.
25 DR. ROHWER: Well, I think I did make it

1 clear that context is everything here.

2 DR. PETTEWAY: Exactly.

3 DR. ROHWER: And you really have to know the

4 context, and you really have to validate what you are

5 doing, or what you are claiming.

6 CHAIRMAN BOLTON: Dr. De Armond.

7 DR. DE ARMOND: I think one of the

8 interesting fallouts from the Weissman study is that

9 certainly prion proteins certainly seems to be -- that

10 the abnormal form of the protein coats this material,

11 this solid material. It is hard to get rid of it.

12 And you can stick it into a brain and it

13 will cause infectivity, which can be a way of

14 assessing the efficacy of cleaning these instruments

15 for batch plasma preparations if you can have a piece

16 of tube that you run your system through.

17 And you then clean it with sodium hydroxide

18 or however it is going to be done, and that can then

19 be inserted into the brain of a susceptible animal,

20 and like a TG bovine PrP mouse, and see whether it was

21 actually clean.

22 CHAIRMAN BOLTON: I hope that you are

23 suggesting that as an experimental study and not a

24 quality control issue.

25 DR. DE ARMOND: I think it could be a

1 quality control issue also.

2 CHAIRMAN BOLTON: I think that might be a

3 bit cumbersome, but you can entertain anything.

4 DR. DE ARMOND: Well, it depends on how safe

5 you want to be. Do you want to know whether there is

6 infectivity there or not, which is the idea. And if

7 you can't measure it by an assay, a standard

8 immunoassay, then a bioassay would be helpful. Then

9 you would at least know the answer.

10 CHAIRMAN BOLTON: I think the difficulty

11 that I would have with that would be if you had meters

12 of tubing, which three millimeters do you take to

13 assay, and how do you validate what does that mean, in

14 terms of a meter of tissue or of tubing.

15 DR. DE ARMOND: At some point, you have to

16 validate whether you have cleaned your instruments

17 properly, and so it could be a one shot deal, but at

18 least it is interesting.

19 And the Weissman study says it is possible,

20 because it is interesting that you can stick just a

21 monofilm of PrP on to a surface, and it will induce

22 the disease in an animal. That is fantastic.

23 CHAIRMAN BOLTON: Stan.

24 DR. PRUSINER: Well, I think that you just

25 cut this meter in two pieces like Bob showed you and

1 assay a thousand animals, right, Bob?

2 DR. ROHWER: Well, the thing is that you can

3 make these measurements. It is just a matter of

4 whether there is enough will to do them.

5 CHAIRMAN BOLTON: Any other questions for

6 Dr. Rohwer? If not, very good. We will then move on

7 to our next presentation.

8 DR. ROHWER: When do we get the pizza?

9 (Laughter.)

10 CHAIRMAN BOLTON: It's not on the schedule.

11 Our next presentation is Dr. Henry Baron, from Aventis

12 Behring, and he will be presenting VCJD Risk

13 Assessment, and Dr. Baron has already spoken with us

14 earlier. So we welcome him back.

15 DR. BARON: The fire bell kind of brings a

16 metaphor to mind. I kind of feel like a fire fighter

17 who shows up with his water hose after the house has

18 burned down.

19 I came here to bring you the take home

20 message that geographic European deferral is not

21 warranted, but of course you a have already

22 exhaustively debated this, and you made a decision

23 about that. However, to err is human.

24 (Laughter.)

25 DR. BARON: If this were Broward County,

1 Florida, I would ask for an immediate and manual
2 recount, but here in the bastion of our democracy, I
3 guess I couldn't pull that off. So what I will try
4 and do over the next few minutes is take the
5 opportunity to show you why you were wrong.
6 (Laughter.)
7 DR. BARON: I would like to do a reality
8 check on this notion of geographic risk with respect
9 to safety of blood and variant CJD. Now, everything
10 that we hear and fear about CJD and blood comes from
11 speculation, conjecture, modeling.
12 But none of this changes the fundamental
13 fact -- and this to me is a key message -- that there
14 is currently no evidence that persons with pre-
15 clinical or clinical CJD -- and that includes variant
16 CJD -- carry infectious prions in their blood, or have
17 transmitted infectious prions through blood or plasma
18 products.
19 Now, therefore this risk remains truly
20 theoretical. This is a statement which was true five
21 years ago, a time when the FDA implemented its first
22 policy of withdrawal and notification for sporadic
23 CJD, when a donor is subsequently diagnosed sometime
24 after his donation.
25 This was by the way a measure that was