DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

68TH MEETING

Friday, March 16, 2001

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Jed B. Gorlin, M.D. (3-16)
Monica Parise, M.D. (3-16)
Susan Stramer, Ph.D. (3-15)
Cees van der Poel, M.D. (3-15)

GUEST

David Wright, Ph.D.

C O N T E N T S

P R O C E E D I N G S

DR. SMALLWOOD: Welcome to the second day of the 68th Meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary of this committee. Yesterday, I read the conflict of interest statement. That statement also applies to the proceedings for today.

If there are any declarations to be made by any of the members, would you please do so now.

Hearing none, then, we will proceed with the agenda and I will turn this meeting over to the Chairperson, Dr. Kenrad Nelson.

DR. NELSON: The opening sessions this morning are a series of updates from FDA committees. The first one will be a Summary of the Transmissible Spongiform Encephalopathies Advisory Committee, which was held January 18th and 19th, by Dr. David Asher.

Committee Updates

Summary of the Transmissible Spongiform Encephalopathies Advisory Committee Meeting

David M. Asher, M.D.

DR. ASHER: Thank you, Dr. Nelson. Good morning.

[Slide.]

I prepared a full summary of the last TSE Advisory Committee meeting with some background material that is on a handout, which will also be available to you through our

CBER web page, and this morning I will just review highlights for you.

[Slide.]

The Advisory Committee addressed four topics. The first and last concern blood safety. The other two, safety of FDA-regulated cells and tissue, and safety of products derived from deer and elk, which are FDA regulated, from herds with chronic wasting disease I will mention only in passing, and I will review only the first topic in detail.

[Slide.]

First, we revisited the issue of blood donors who had been in BSE countries, that is, whether to defer them. As you may recall, unlike other forms of Creutzfeldt-Jacob disease, in new variant Creutzfeldt-Jacob disease, the abnormal protease-resistant prion protein accumulates to substantial levels in lymphoid tissues, a finding that early on raised concern that the relatively reassuring epidemiologic evidence suggesting that blood was unlikely to be an important vector for classic forms of CJD might not be predictive for variant CJD.

[Slide.]

That prompted CBER's current policy of recommending deferral of donors resident in the UK, the United Kingdom, for any cumulative six-month period from the presumed start of the BSE epidemic in 1980 to the full

implementation there of a series of measures to prevent human exposure.

[Slide.]

Cases of BSE continued to fall in UK cattle although over 1,300 cases were recognized there last year.

[Slide.]

Since the end of 1997, the USDA has considered cattle in almost all other European countries to have been potentially exposed to the BSE agent, and FDA relies on USDA in those decisions.

Rates of new cases and deaths from both new cases and deaths from new variant CJD have continued to rise in the United Kingdom, and evidence suggests that in some other European countries, a substantial part of the supply of beef and beef products may have come from the UK, presumably causing the cases of new variant CJD seen in three French patients who have no history of actual travel to the UK.

Recently, cases of BSE have increased in cattle in France and in several other European countries and new countries have recognized BSE in native animals, raising concern that in addition to exposure to UK beef products, exposure to indigenous BSE may have become another important source of human infection.

[Slide.]

Since I summarized the situation before this

committee last summer, three more countries, Germany, Italy, and Spain have found cases of BSE in native cattle. Germany found 17 more cases just since I made this table a couple of weeks ago, so that at present there are 13 definite BSE countries and 18 more suspect countries on the USDA list.

[Slide.]

The reported transmission of BSE with blood of a sheep experimentally infected with the agent also increased our concern that blood of persons incubating new variant CJD might also serve as a source of infection, and there are other concerns listed here.

[Slide.]

The committee reviewed information about new variant CJD and BSE in Europe, Canada's risk assessment leading to the decision there to defer donors resident in France as they do for UK, potential exposures of U.S. military and their dependents to UK beef in other European countries, and finally, possible effects that various new deferral policies might have on the U.S. blood supply.

[Slide.]

We asked the committee to evaluate the new information and to consider possible new efforts to reduce the risk that some donors might be infected with the BSE agent, as well as the implications that any new deferral policies might have for the blood supply.

We put five questions to the committee, and I will briefly summarize the advice that they offered in response to each question. As most of you know, on the day before the meeting, the American Red Cross had issued a press release describing a proposed new deferral policy regarding donor residence and travel in BSE countries, and the TSE Advisory Committee members were clearly aware of that announcement.

[Slide.]

Nevertheless, the committee advised no change in the current FDA recommendation to defer donors resident in the UK for six months or more. The members all seemed relieved that the policy had not resulted in any detectable shortage of blood in the U.S.

[Slide.]

A majority of members advised deferring donors resident in France for 10 years or more from 1980 to the present, and accepted the idea first put forward at last year's June meeting that exposure of the French population to UK beef during years of high prevalence of BSE in the UK might have been about 5 percent of that in the UK itself.

The number of new variant CJD cases in France as of last year had also been about 5 percent of those in the UK, but fortunately, the number of recognized French cases has not increased since then.

[Slide.]

In response to our third question, which included a proposal to defer donors resident in other BSE countries for the same period that they had advised for France, that is, any 10-year aggregate residence after 1980 through the present, they overwhelmingly declined to do so, persuaded that potential exposures to UK beef were smaller in other European countries than in France, and that except for Ireland, none of those countries had recognized a case of new variant CJD.

[Slide.]

But because of growing concern about possible human exposures to BSE agent from other non-UK beef, a very closely divided committee went on to recommend that the proposed deferral policy be recommended, but only for those two countries with the largest numbers of cattle diagnosed with BSE outside the UK, namely, Portugal and the Republic of Ireland.

[Slide.]

They also declined to advise deferring donors for a combined period of residence in more than one country because they worried that tallying combined exposure would be logistically difficult and fraught with error. One member who favored the idea because it seemed logical suggested a simple way to do that and proposed a pilot study

of a modified donor questionnaire be considered.

[Slide.]

Finally, a majority of the committee also advised against treating donors potentially exposed as active duty U.S. military or as dependents in Europe to substantial amounts of beef products from the UK estimated on some bases at certain times to have been perhaps 20 to 35 percent of the total supply, be deferred as if they had been in the UK for the same period of time.

[Slide.]

They did, however, advise the FDA to develop some less stringent policy for deferring U.S. military donors presumably those exposed for longer periods of time than six months.

They suggested first attempting to estimate the effects that various deferral policies might have both on the military blood program and on civilian programs where many military retirees and former dependents live.

[Slide.]

Let me conclude by alluding briefly to the three other topics that the TSE Advisory Committee reviewed.

They next addressed the issue of CJD risk and other human cells and tissues regulated by the FDA should deferral criteria similar to those for blood apply. They unanimously agreed that there is a risk of transmitting new

variant CJD, such transmissions already having occurred with classic CJD through dura mater allografts and corneal transplants.

Consequently, the committee members were most concerned with those materials. They felt that the theoretical risk from bone marrow-derived cells, which are very hard to match and have a high potential benefit for patients with life-threatening diseases, was less troubling. A majority of members endorsed FDA's continued efforts to develop a donor deferral policy for regulated cells and tissues.

Ruth Solomon, who is to be our next speaker, organized this session and will be available to answer questions about that topic.

[Slide.]

The committee generally agreed that in both wild and domesticated cervid animals, that is, deer and elk, chronic wasting disease clearly spreads by contact and that animal tissues must contain the infectious agent, however, available evidence fails to suggest that transmission of infections to humans has occurred.

The committee declined to speculate about whether the agent of chronic wasting disease has the potential to infect some humans.

[Slide.]

Finally, the committee concluded that except for BSE, none of the other TSE agents of animals has been demonstrated to infect humans and that no deferral of any donors exposed to such agents is indicated although they encourage continued surveillance of humans exposed to the animal agents.

Members were concerned that bovine materials found in some dietary supplements could conceivably introduce the BSE agent into the United States and expose humans to the agent although that is not known to have happened.

[Slide.]

Let me close by listing the various animal TSE agents to which humans may be exposed and the committee's estimate of the appropriate level of concern about the various agents with the reasons for those conclusions.

I will end there and I thank you very much.

DR. NELSON: Thank you, Dr. Asher.

Are there any questions or comments? Yes, Dr. Simon.

DR. SIMON: I guess the obvious question, has FDA determined a policy and when might we expect to see it promulgated and distributed?

DR. ASHER: A policy is in development and I would never in the presence of senior management predict.

DR. EPSTEIN: Thank you, David.

FDA's current thinking is to go forward with a draft guidance consistent with the Advisory Committee recommendation concerning France and concerning Portugal. We would like to reconsider the issue of Ireland and more generally develop what we hope would be a coherent and risk-based strategy to deal with the ongoing BSE epidemic in Europe.

So, what we would hope to do is bring forward a draft for comment in the near future. It is hard to be precise. It is still being developed internally. We also are working with DOD to come up with a strategy to propose on deferral for active duty servicemen and dependents who may have been exposed to UK beef in the risk period.

DR. SIMON: That is only active duty that that would apply to?

DR. EPSTEIN: No, no, no. The deferral would be because they were exposed.

DR. SIMON: In active duty.

DR. EPSTEIN: Right.

DR. SIMON: So, it would apply to the civilian sector, as well.

DR. EPSTEIN: Yes, when they come back and they are civilians, they still have that exposure history.

DR. NELSON: The other thing that I remember from that meeting is that although the data are not sufficient to

predict how many cases might occur, various opinions and modeling, et cetera, suggested that the total in the UK might end up being in the hundreds rather than hundreds of thousands, but it is really with the incubation period and the long exposures, it is hard to be sure on that. I think the total is 92 now?

DR. ASHER: It is over 90 in UK and still 3 in France, 1 in the Republic of Ireland in a person who lived in the UK for six years. Considering that the number is already over 90 just since 1996, I think it is very unlikely that the final number will be in the low hundreds, I think it is likely to be more than that. Cases of Kuru have continued to occur more than 38 years after the last exposure in cannibalism.

Of course, we have only seen subjects homozygous at codon 129 of the prion protein and coding gene. We don't know what the incubation period might be should other genotypes prove to be susceptible.

DR. NELSON: The FDA has received a letter from the Dutch in which Dr. Smallwood would like to read into the record.

DR. SMALLWOOD: For the record, the committee members have received a copy of a letter from the New York Blood Services from Dr. Paul Stringers at the CLB Blood Bank in Amsterdam, the Netherlands. The subject of this letter

is that they feel that extending the ban on British donors regarding new variant CJD and BSE to all Western European countries is not justified. This letter is posted on the FDA web site.

Thank you.

DR. NELSON: The next report will be a report by Dr. Ruth Solomon on Tissue and Organ Regulation.

Office of Inspector General Report

on Tissue and Organ Regulation

Ruth Solomon, M.D., IOD, OBRR

DR. SOLOMON: First, some background. Last spring several articles appeared in the Orange County Register and the Chicago Tribune that raised concerns about the tissue banking industry, for instance, the informed consent process to donate tissue, the current level of oversight, the lack of a system to monitor tissue supply, and the apparent profiteering by some tissue banks.

These articles came to the attention of the Department of Health and Human Services and last summer many briefings were held with federal agencies, professional organizations, the industry, and donor family groups.

The Department requested that the Office of the Inspector General investigate and report on two areas - oversight and informed consent. In January of this year, OIG published its two reports. I will review their

recommendations.

[Slide.]

The first report was entitled, "The Oversight of Tissue Banking."

[Slide.]

The recommendations were made to the Food and Drug Administration. The first recommendation is that FDA should expedite the publication of its regulatory agenda that requires registration of tissue banks, enhanced donor suitability screening and testing, and the use of good tissue practices.

FDA has published a final rule on registration, which is to go into effect April 4th. We have also published two proposed rules, one on donor suitability, which published September 30, 1999, and another on good tissue practices, which published January 8th of this year, and the comment period for that is still open.

[Slide.]

The second recommendation was that within its existing regulatory authority, FDA should take two steps to enhance oversight of tissue banking.

[Slide.]

First, FDA should set a realistic, yet aggressive, date by which it would complete an initial inspection of all tissue banks.

Secondly, FDA should determine an appropriate minimum cycle for tissue bank inspections. Usually these are biennial, every two years.

Since the regulation of tissue banks is an unfunded mandate, FDA has had to take resources from other areas to accomplish the inspections, and FDA is responding to this recommendation by prioritizing inspections and reinspections.

[Slide.]

The third recommendation to FDA was that it should work with states and with professional associations that have inspection and accreditation programs to determine in what areas, if any, oversight activities could be coordinated. Currently, there are two states, New York and Florida, that have inspection and accreditation programs.

FDA is carefully evaluating this recommendation on how to best assure adequate inspection coverage and work with other groups through an exchange of information.

[Slide.]

The second OIG report is entitled, "Informed Consent in Tissue Donation, Expectations and Realities." These recommendations were not addressed to FDA because FDA's regulations do not address obtaining informed consent. Rather, the recommendations were made to other departmental agencies and to the industry.

[Slide.]

Firstly, a recommendation was made to the Health Resources and Services Administration, HRSA, that they should work with groups representing donor families and the tissue banking industry to develop guidelines for conveying information to families about tissue donation.

[Slide.]

The second recommendation was made to the Health Care Financing Administration, that they should address informed consent for tissue donation through the Medicare conditions of participation for hospitals and for organ procurement organizations.

The Medicare conditions of participation are regulations where a hospital must assure that the family of each potential donor is aware of their donation options.

[Slide.]

The OIG then made four recommendations to the tissue banking industry concerning informed consent. The first one said that at the time of obtaining consent, tissue banks should provide families with written materials that provide fuller disclosure about the uses of tissue and the nature of the gift.

Industry has already implemented this recommendation by issuing in November of last year the AATB, EBAA, and the Association of Organ Procurement organizations

issued a joint model elements of informed consent that contained certain basic elements and certain additional elements.

[Slide.]

The second recommendation to industry was that tissue processors and distributors should ensure that information accompanying their product clearly indicates it is derived from donated human tissue.

It was felt that this would just represent a minimum change in the packaging and marketing of tissue.

Currently, no FDA requirements for labeling exist.

[Slide.]

The tissue banks should foster greater accountability for the performance of those who request consent for donation, both their own employees and those that they contract with at hospitals. This would include training, retraining, and assessment of those performing the informed consent process.

[Slide.]

Lastly, the tissue banking industry should work with representatives of groups representing donor families to explore a process for periodic public disclosure about tissue banks' financing, that is, profit or nonprofit.

Under this recommendation, the tissue bank industry should consider whether financial information would

be useful to the family, the advantages and disadvantages of disclosing this, and what impact it might have on donation, should the information be provided or only if requested, and the content, style, and format of the disclosure.

Thank you.

DR. NELSON: Thank you very much.

Are there questions?

DR. STRONCEK: My understanding is we have blood banks, which is one regulatory group, and then there is stem cells and bone marrow, umbilical cord blood. My understanding, you are not considering that tissue, that is a separate regulation?

DR. SOLOMON: That is correct. First of all, bone marrow that is minimally manipulated is not even regulated by FDA, but the other two, umbilical cord blood and peripheral blood stem cells are being regulated under the tissue approach rather than under the blood approach.

DR. STRONCEK: And then organs are separate or is that regulated under tissue?

DR. SOLOMON: Organs are not regulated by FDA. They are regulated by HRSA.

DR. STRONCEK: Thank you.

DR. NELSON: The next presentation is by Dr. Stephen Nightingale, the Executive Secretary of the Advisory Committee on Blood Safety and Availability.

Summary of PHS Advisory Committee Meeting

January 25-26, 2001

Stephen Nightingale, M.D.

DR. NIGHTINGALE: Thank you very much, Dr. Nelson.

[Slide.]

On the first slide, I have it up here simply to comment that this was the 13th meeting of the Advisory Committee on Blood Safety and Availability. We do not have the lineage that you do, but we have arrived at our adolescence and it is perhaps fitting, because perhaps only an adolescent would have had the courage to tackle the topic which is on the next slide, which was How Should the Government Respond to the Current Debate over Universal Leukoreduction.

The meeting was held on January 25th and 26th.

[Slide.]

Those of you who are aware of your own lineage will recall that this topic was in fact discussed by the Blood Products Advisory Committee on September 18th of 1998, and there were extensive discussions within the Department about whether and, in fact, certainly how this should be brought to the Advisory Committee.

I have here on the slide the initial paradigm which was that at the Blood Products Advisory Committee, the issue was the benefit to the risk and perhaps at the

Advisory Committee, the paradigm would be the ratio of benefit to cost, but neither I think really captured the essence of the debate, and I think that was why the debate only came to our forum.

[Slide.]

It came really as a town meeting. We spent a lot of time figuring about how to fit societal issues into our paradigms, I think to the extent that we were successful at this meeting it is because we dropped the paradigm for a moment and said let's talk about it.

[Slide.]

In fact, when we said let's talk about it, the issue as it had come out of the Blood Products Advisory Committee, had been framed by many as an issue of cost.

Dr. Leo McCarthy of Indianapolis, one of the few people who was invited who was unable to make it, had commented at one public debate on the issue when somebody says it is not about cost, it is about cost, and I think Dr. McCarthy's point was very well taken, but I think it did not capture the entire debate.

Not just to make light of Leo's point, but there was more to it - was it cost, was it science, was it something else, so we decided to let the good times roll or the debate roll, so to speak, and how we did it is initiated on the next slide.

[Slide.]

We started out with an expert panel. We were very fortunate to have both Dr. Mo Blajchman and Dr. Steve Vamvakas--I know that is not his first name, but I do not pronounce it well, and he goes by Steve to me--co-chair. They are the authors of an extensive, very thoughtful review of the issue which will be published in an upcoming issue of Transfusion.

We were equally fortunate to have the services of Dr. Harvey Klein, Dr. Ed Snyder, Dr. Walter Dzik, Dr. Jim AuBuchon, Dr. Jerry Sandler, and Dr. Paul Ness. They were asked to present their own perspective rather than the perspective of a particular institution, and they did so with moderation by Dr. Blajchman and Dr. Vamvakas.

[Slide.]

We were again fortunate to have comment from Ms. Frederick of the Red Cross, Dr. Bianco, Dr. Jeff McCullough. We had representatives of Baxter, HemaSure, Pall, and Terumo, the University Health System Consortium, the American Hospital Association.

[Slide.]

Dr. Goldfinger, Dr. Blumberg, Dr. Moore, Dr. Sayers, representatives of the Committee of Ten Thousand, Hemophilia Federation of America, National Hemophilia Foundation, and Immune Deficiency Foundation.

[Slide.]

After the presentations and discussion, the committee quite on its own came up with the following consensus statements, which I think are very useful as placemarkers for where the committee was going, and I think it is possible to trace where the committee went from these consensus statements.

The first, with a few exceptions, prestorage leukoreduced blood is not inherently dangerous to the recipient. Second, there is agreement that leukoreduction is beneficial for some patients by reducing the number of febrile events, CMV transmission, and alloimmunization.

[Slide.]

Third, the evidence is not conclusive that leukoreduction reduces postoperative infections or reduces malignancy in unrecognized immunodeficient patients.

Fourth, the likely benefits of universal leukoreduction include averting consequences of failure to identify those who may require leukoreduced products in reducing the likelihood of administration of incorrect blood products.

[Slide.]

Finally, areas of contention regarding universal leukoreduction include cost, effect on supply, compromising future investigations, and regulatory burden.

[Slide.]

Upon completion of that, there was vigorous discussion, and the following recommendation was adopted, that universal leukoreduction should be implemented as soon as feasible.

[Slide.]

In addition, the Advisory Committee recommended that in regard to universal leukoreduction, the Advisory Committee is concerned about the availability of blood and the resources necessary to implement universal leukoreduction. For these reasons, the Advisory Committee recommends that the actions of the Department of Health and Human Services should strive to: minimize the impact on supply, assure adequate funding for this effort, issue a regulation to implement universal leukoreduction that addresses these concerns, and report to the Advisory Committee on a regular basis the progress toward these goals.

[Slide.]

Final recommendations. Given the unresolved scientific issues in the field, the Advisory Committee supports continuing research on the effectiveness of universal leukoreduction.

Last, in the above resolution, the word "leukoreduction" is intended to mean prestorage

leukoreduction, and the resolutions refer to non-leukocyte cellular blood components.

I believe that the members of the Blood Products Advisory Committee have received a copy of the summary of the meeting. That summary is posted on the web site, and it will be published in a future issue of transfusion.

I would be glad to answer any questions.

DR. STRONCEK: There has been a draft guidance issued by the FDA concerning universal leukocyte reduction. It alludes to a number of abstracts that suggest that the filters simply don't work for everybody, that there is potentially problems with people with sickle cell trait, and the guidance suggests that people with sickle cell trait be excluded from donating.

That seems to me to be kind of an odd stance. I would think that there would be pressure, you know, rather than tell the blood banks you can't collect blood from a certain population, that you tell the manufacturers to find out what is going on and fix their filters.

Do you know what is going on with any of this?

DR. NIGHTINGALE: I am really not the right person to comment on that one. I would defer to Dr. Epstein.

DR. EPSTEIN: That is, of course, FDA's guidance. Yes, there is a task force that has been put together including government agencies, scientists who do active

research in this area, and filter manufacturers, to try to solve the problem technically.

The problem is what do you do in the meantime, but it is draft guidance, and it is not yet out for implementation, and we are hoping that a solution can be found.

DR. STRONCEK: Well, somebody in the government license these filters. My understanding, there is a considerable profit made on the filters. You know, as an end user, I just can't see where we are very tolerant with the manufacturers for not putting extensive resources into this problem and why does government money have to go into it, why aren't they solving it on their own.

DR. NIGHTINGALE: Maybe I could come back to the microphone here. Dr. Epstein and I have perhaps overlapping jurisdictions here, and I think our jurisdictions overlap here in our lack of jurisdiction. The government is not all powerful. There are reasons for that.

DR. STRONCEK: Well, if we have a problem with the blood product, that has got to be recalled and fixed. You know, I think there is a serious problem with a device here and rather than tell the manufacturers they have to fix the device, the message is there is a crummy device out there, so the industry has got to use that device and potentially lose donors.

I would think that we, as government agencies, are going to push for universal leukocyte reduction, we also better use everything we can in our power to make sure we have the right tools to do it.

My understanding is these filters are licensed. Why are you being so gentle with the manufacturers and suggesting that they look into this and have a committee, why don't you put some pressure on them as far as their licensure?

DR. EPSTEIN: Well, we cannot de-license a product that meets its licensed standards. In other words, what would be the basis to revoke licenses or actually device approvals in this case? That mechanism doesn't exist unless we thing that the products are found to present a safety hazard in their own right, there is something wrong with them.

This is not to say that we aren't putting pressure on the companies, but I think you shouldn't underestimate the power of the market force. If the user community makes clear the sentiment to the filter manufacturers that they will prefer to purchase any filter that meets a higher standard and doesn't have this problem of failure with sickle trait, then, it is a clear signal that there is a market demand for modified product.

That is at least as powerful a force as the FDA

pounding on the table and saying we want a better product, but I think what Steve was saying, and what I was trying to say, is we have no mechanism to compel that. I mean somebody has to want to make it and validate it.

DR. STRONCEK: The standard of clinical trials today is that you can't just--you do a clinical trial on one racial group, you have to enroll patients in clinical trials with a variety of different racial groups.

It is hard to believe this problem didn't come up if the manufacturers really tested their device among people of many different racial groups, so I think they do have a faulty problem if that is the case, and there is reason to hold their feet to the fire to get this thing fixed, this problem fixed.

DR. OHENE-FREMPONG: Just as a follow up, it sounds easy to say that you will exclude people with sickle cell trait from donation, but to my knowledge, most blood collection groups don't test people who are volunteering to donate for the hemoglobin type, and that is only at the user end, that blood, that may be from an AS individual, may be excluded for a particular patient.

The effect of this, it would seem to me to try to exclude up front all those who may be in the populations that may have sickle cell trait as a high incidence because as it is now, I don't think donors are tested for sickle

cell trait before they donate blood.

DR. EPSTEIN: Our guidance does not recommend that persons with sickle trait be deferred. What we are recommending is that screening be done, so that appropriate monitoring can be done of leukofiltration. Not all persons with sickle trait would fail leukofiltration. Additionally, such persons could donate by apheresis or could become dedicated plasma donors.

So, it is a misunderstanding of the guidance to interpret it as precluding donation, that would not be true. What we are saying is that at the moment, it is an uncontrolled variable relating to the quality of filtration. We know that there is a high likelihood that residual leukocyte count will be not be reduced if the donor has sickle trait.

So, what we are saying is you have to be mindful of that and manage that situation. Now, in some cases it would preclude being a donor of a leukocyte reduced cellular product, however, that product could be leukocyte reduced by other means than filtration.

So, it is not a 1 to 1 equation. I realize that at a pragmatic level, it might be easier for some centers simply not to accept the donation, but the guidance doesn't actually say that, and I agree with Dr. Stroncek's point of view. We would much rather see the filters fixed. What we

are really talking about is how do we get there.

DR. SCHMIDT: There is a clinical problem which can never be fixed on the biological differences between how much hemoglobin is in a bag of blood and how much of it is in viable red cells, and this is something that is generally ignored by the clinician, and not appreciated, but if in leukoreduction we lose an additional 10 percent of the red cells routinely, if that is the proper number, then, we are throwing something else into the mix.

I don't know how the clinicians would be advised of that or it is really a labeling question, but the variability was that some bags had more and some bags had less, and now we are getting into a situation where all bags have less, so it is a little different from the biological variability of the donor.

DR. NIGHTINGALE: Yes. I think I would simply comment that the point that you raised and the points that Dr. Stroncek raised previously were considered by our Advisory Committee, as I believe they were considered by you two years ago.

DR. NELSON: Thank you.

The next topic on the agenda is guidance on malaria exclusions, applicability to plasma. The first speaker will be Dr. Mark Heintzelman from the FDA.

IV. Guidance on Malaria: Applicability to Plasma

Introduction and Background

Mark Heintzelman, Ph.D., DBA, OBRR

DR. HEINTZELMAN: Thank you.

[Slide.]

Well, here we are, sandwiched in between the Ides of March and St. Patrick's Day. It is very hard to look to history to find a memorable event to note for today, but I did hear on WGMS this morning that it was 151 years ago that Hawthorne wrote and published "The Scarlet Letter." I think that leaves us room. So, thank you, Doctor.

We are here today to discuss an interesting proposal for a variance that has come to the Center for Biologics. The topic is Guidance on Malaria: Applicability to Plasma.

What I would like to do is to read a brief prepared statement that is essentially the issue paper that was sent to the committee. I do that for the benefit of the audience that may not have had a chance to look at our web page.

So, with that in mind, before I go to the slides, the issue is: Is there a significant risk of malaria from transfusion of frozen plasma products collected from donors at risk for malaria?

The background is currently, the Code of Federal Regulations, which would be citation 640.3(b)6 for those of

you so inclined, prohibits the collection of whole blood and blood components from donors at risk for malaria. This is not true for source plasma for further manufacture, where malaria risk is excluded from donor criteria, however, plasma derivatives are processed in a manner that eliminates parasites. Historical data suggest that the risk of transfusion-transmitted malaria from frozen plasma products is low, if it exists at all.

In a draft guidance document published on January 13, 2000, FDA proposed updated recommendations for deferral of donors with risk of malaria to be applicable to donations including intact red blood cells or platelets.

In preparing to issue its final guidance, FDA needs to clarify its policy on use of frozen plasma products when a donor has risk of malaria.

The issues for discussion. In a request for variance to the Code of Federal Regulations, the FDA has been asked to review its current policy of requiring plasma donors to be deferred if they have traveled to a malarious area. The specific request asks that donors at risk for malaria be allowed to donate plasma products by a specific automated apheresis method using the Autopheresis C device.

These products will be frozen and thawed prior to use for transfusion. These products include fresh frozen plasma and cryoprecipitate. It is also requested that use

of apheresis plasma, relabeled as recovered plasma for further manufacturing, also be permitted in the face of malaria risk.

FDA therefore seeks to clarify whether it should permit exemptions to the regulations to permit collection of blood and components to make frozen plasma products despite malaria risk in the donor.

Currently, when a post donation information report of malaria risk is received, the FDA requires removal from inventory and distribution of any cellular components or fresh, never frozen, plasma products. This is consistent with the guidance published in an FDA memorandum dated July 26, 1994.

However, in its 1994 guidance, the agency did not explicitly recommend the removal from inventory or distribution of frozen plasma products, and some centers have released these products for transfusion. Consistent with the Code of Federal Regulations, a donor history positive for malaria risk would have precluded collection of blood components. FDA therefore seeks to clarify whether it should continue its current policy that allows these products to remain in inventory and be released for transfusion.

In order to gather this data, I am going to try to put the picture together for you in order to come to a

logical conclusion based on the data presented to you, we will approach it in this fashion.

The issue to be discussed is the malarial risk for frozen plasma products for transfusion, the laboratory and epidemiological evidence for and against that risk will be presented, and the practical effect of the FDA policy on product availability will be discussed.

With that, I would like to go to the slides.

[Slide.]

So, the issue to consider: Is there a significant risk of malaria from transfusion of frozen plasma products collected from donors at risk for malaria?

[Slide.]

The FDA is being requested to consider a variance to the Code of Federal Regulations to allow collection of plasma by apheresis from donors that have traveled to malarious areas.

[Slide.]

Title 21 of the Code of Federal Regulations 640.3(b)6 is where we find the regulation that addresses the issue of malarial risk. It is found in Whole Blood Suitability of Donor, Qualifications of Donor.

Within it, it states, "Freedom from any disease transmissible by blood transfusion insofar as can be determined by history," and that would include questions

regarding travel to a malarious area and examinations as indicated further above in the regulations. So, that is where we find the first indication.

[Slide.]

Next, in the Code of Federal Regulations, Title 21, 640.3(b), under Plasma, we find the specific mention of "plasmapheresis donors shall meet the criteria for donor suitability prescribed in 640.3," which is the source plasma for further manufacture citation, "excluding the phrase other than malaria," meaning that plasma donors, even plasmapheresis donors, shall be questioned to determine malarial risk in paragraph (c)(9) of the section.

So, I am trying to link this firmly to a rooting in the regulations, and that is the reason that we can then accept a request for variance to this if the data support it.

[Slide.]

Our current policy. Many of you are aware that we have a proposed 2000 draft policy, but we have had a current policy in effect all along, that is, our July 26, 1994 document. Within that, we find a statement, "These recommendations apply only to donations containing intact red blood cells. Donations used for preparing plasma, plasma components, or derivatives devoid of intact red blood cells are excluded."

Now, this appears a little difficult when you look at the requirement in the regulations that this is not acceptable, the donor, even for plasmapheresis will be screened. We are here to seek clarification to this.

[Slide.]

Just a brief update. How are we going to get the data to be able to make this ascertainment? Dr. Chiang Syin will review viability of malaria parasites in plasma, which will essentially be the laboratory studies.

Dr. Monica Parise from the CDC will review transfusion-transmitted malaria in the United States focus on fresh frozen plasma.

Dr. Jed Gorlin will present plasmapheresis from donors deferred for malaria travel.

I would like to point out that we are very fortunate to have this team put together to do this work. We have a highly qualified group about to make these presentations, and it is a unique opportunity.

The questions to the committee will be:

1. Are the available scientific data sufficient to conclude that it is safe to prepare frozen plasma products for use in transfusion despite a history of malaria risk in the donor (a) when the plasma is prepared by separation from whole blood; (b) when the plasma is prepared by automated apheresis (any method); (c) when the plasma is

prepared by apheresis using the Autopheresis C device?

The last question to the committee: Balancing the risks and the impacts on supply, should FDA continue its current policy to allow use of frozen plasma products for transfusion when the donor provides post-donation information positive for malaria risk?

As you go through the presentations, now you know what it is we are going to ask you.

Any questions?

DR. NELSON: Questions?

Do you differentiate malaria risk meaning travel and malaria illness meaning a person who has had malaria, or are they both the same?

DR. HEINTZELMAN: We differentiate those in our memoranda, both the current memoranda that is in effect and the proposed memoranda address specifically those who have had malaria are deferred, and then separate sections identify the risks of travel to those areas.

Now, are you implying that within our framework as proposed, doing our analysis for this variance request, would someone who has had malaria and been treated effectively and recovered still be allowed to do this, is that the essence of your question?

DR. NELSON: Treated effectively or not treated effectively, maybe not with a radical cure or whatever. I

mean I am just wondering if you are differentiating malaria risk from malaria or are they all in the same?

DR. HEINTZELMAN: As is currently proposed, we would not consider these to be different based on the variance request and the information we have. You know, the infectivity of malaria is going to be associated with red cell contamination . Clearly, a major impact on what we will cover today will be what the residual red cell risk is in plasma collected by apheresis, and the survivability of red cells and Plasmodia after freezing.

It is interesting to note that there are a number of people who can donate blood in the United States that may have had malaria and may very well not be aware of their infectivity state, and I think that Dr. Parise has presented in prior sessions information about.

That is where we are getting our cases of malaria now, but I am almost positive that it is just about exclusively associated with cellular donations and transfusions, not with plasma. I think Monica will have more information on that.

DR. CHAMBERLAND: I guess I am trying to seek further clarification as a follow up to Dr. Nelson's question. If I heard you correctly, Mark, I believe you said that the question includes both history of malaria risk or actual malaria, people who have actually had malaria.

Unless things have changed, the information that the committee got from Dr. Gorlin was that the variance that his blood bank was applying for was for travelers, not those who have had malaria.

So, is FDA proposing to go beyond that and make it even more comprehensive?

DR. HEINTZELMAN: We are proposing to look at the variance that has come to us to determine that. This is one of the issues to look at today and to consider as we go forward.

DR. CHAMBERLAND: So, then the variance request applies only to travelers, not those who have had malaria?

DR. HEINTZELMAN: Dr. Gorlin is shaking his head yes.

DR. EPSTEIN: That may be true of the variance request, but we are asking more broadly how we should deal with malaria risk as an exclusion for preparing frozen plasma products for transfusion. That is really what we are asking because we have to look more broadly. This particular variance request is narrow, the next one might not be.

DR. CHAMBERLAND: So, the FDA question to us is both, it applies to travel, as well as individuals who give a history of having had malaria?

DR. EPSTEIN: Yes. If the committee thinks that

the answer should be stratified, you know, we will hear that from you, and that is an important point.

Now, I don't think we are saying that anyone who contemplates drawing blood for making components from someone actively ill, you know, we are not saying having malaria, but we didn't stratify the basis of risk in the question. There are different criteria that indicate risk, but I think from a scientific point of view, it is really the same, because what we are saying is if there was a risk factor, the presumption has to be made that the donor might be asymptomatically incubating malaria. In other words, you have to presume that malaria may be there in order to answer the scientific question of whether the products are safe.

DR. KOERPER: Dr. Epstein, what is the current regulation for deferring an individual who has had clinical malaria?

DR. HEINTZELMAN: We specifically in our current regulation point out as one identifiable category that these people are deferred. The current regulation doesn't talk about treatment.

DR. EPSTEIN: It is three years, three years from the last treatment, and that is recommendation, not regulation. The regulation, as Dr. Heintzelman showed, is freedom from a transfusion transmissible disease, but the guidance recommendation is three-year deferral after

resolution of active malaria.

DR. HEINTZELMAN: Right, it doesn't talk about treatment.

DR. NELSON: The next presentation, Dr. Chiang Syin from FDA.

Chiang Syin, Ph.D., DETTD, OBRR

DR. SYIN: Good morning.

[Slide.]

Today I will go over briefly some of the historic data regarding the viability of malaria parasites in blood and plasma stored under freezing temperature, because this is relevant to what the variance is. This subject is of particular concern on the potential risk of acquiring transfusion-transmitted malaria through plasma products.

[Slide.]

It has been well established that malaria could be induced by transfusions through the following cellular products including whole blood, packed red cells, platelets, leukocyte concentrate and one extra one is the liquid of fresh plasma.

Malaria parasite is an intra-erythrocytic protozoan which propagates within the red blood cells after invasion by a merozoite. The merozoite, I should remind you, will develop within the red cell into a ring form and slowly progress to a trophozoite and to a schizont, and

finally it was segmented into multiple merozoites and ruptures the host red cells to release more merozoites into the blood stream for the next cycle of invasion and growth.

[Slide.]

In contrast to the previously mentioned product, frozen plasma products such as cryoprecipitate and fresh frozen plasma are generally considered safe because you can see, in reading many historical references, especially a serious review article by Leonard Bruce-Chwatt in the '70s and '80s, they point out that there has never been any incident report of transfusion-associated malaria implicated by those products.

However, when we received the various petitions from Dr. Gorlin, who went through the literature search, he found out that, in 1985, Wells and Ala of NBS, UK, published an article on transfusion malaria implicating cryoprecipitate without any direct reference or supporting data. I have not been able to find a similar reference in the literature implicating a frozen plasma product.

To try to further clarify this issue, I have sought the help of a British colleague in NBS to try to track down those authors. Unfortunately, Ms. Wells left NBS in 1987 and Dr. Ala retired in 1990. So, over the last several months, we finally tracked down Dr. Ala through the help of a British colleague and I have a few communications

with Dr. Ala about this issue.

Dr. Ala pointed out, on February 13, in his e-mail to my request--he mentions what he stated before in the Lancet article is circumstantial and speculative and draws from his own personal experience which is based on one patient he has helped to manage. This is a young, severe hemophiliac patient undergoing lung surgery to remove a bleeding cyst.

He said he only used the cryoprecipitate, the home-made cryoprecipitate he personally made and the fresh frozen plasma to combat the bleeding problem. In this conversation, at the end of his e-mail, he did recognize he cannot claim either cryoprecipitate or fresh frozen plasma, FFP, could be implicated in this case because he really doesn't have other data to suggest.

However, he also mentioned in some of the personal experience he has dealing with the malaria parasite inside red blood cells. He noticed, in the frozen plasma, sometimes they could find a lot of red cells. When they go through freezing and thawing, they could actually detect intact red blood cells with the ring form inside which appears to be viable, even though he did not do any experience to substantiate.

This is a very interesting fact because my own experience was in vitro culture with Plasmodium falciparum.

We pretty much see similar things. The more mature stage merozoite parasite within the red blood cell usually will not tolerate the freezing and thawing except in the ring stage.

So, based on that, I started to look into other literature. Before I get into the next slide, I would like to talk about some of the factors contributing to the viability of malaria parasites. We should consider the host red blood cell, the state of the host red blood cell, its age, its integrity, and some effect of intact coagulins or preservatives, and also the effect of temperature, especially undergoing freezing and thawing.

The other point that we should consider is the stage of the parasite. Just like I mentioned earlier, most of the time, only the young ring stage will survive through this process.

[Slide.]

The viability of the malaria parasite was mostly studied during the early to mid-1900s due to the high incidence of transfusion-transmitted malaria during the first half of the century. Parasites were used to induce malaria as a therapy for neurosyphilis or general paresis or to test chemotherapeutic in volunteers.

This practice largely disappeared due to two factors. One is the introduction of penicillin and the

disappearance of syphilis from patients in the U.S. The other thing is, in 1960, the development of using a primate model to harbor or propagate the human malaria parasite has been very successful so the use of inoculating a human volunteer has pretty much stopped.

The study I am going to cite is concentrated in the whole blood preservation and only one reported in the plasma.

[Slide.]

When we talk about parasite viability in the plasma and we look at the literature, it is very interesting. In 1930 to 1940, there is a lot of literature talking about various ways to try to preserve the parasite in whole blood. There is only one plasma study we could find which was conducted by Lozner and Newhouser and published in the American Journal of Medical Science in 1943.

What they did is they took citrated blood and separated the plasma, plasma collected from donors with active malaria and injected it into patients. These are human volunteers. Their results is they did not find any infection in recipients, 23 recipients.

Twenty volunteers received frozen plasma and three received freeze-dried plasma. Out of the other twelve volunteers, they separated them into three groups. The

first group has been injected with one-day-old plasma. The second group received one-week-old plasma. The third group received two-week-old plasma. All this plasma we are talking about in this group is liquid plasma.

They found, in the first group of two volunteers, one definitive infection. One is a probable infection. The reason is this patient has, five years previously, been infected with malaria before, so they cannot exclude that possibility that it is due to a previous infection.

In the one-week-old population, they did find one showed parasitemia in the smear. They went back to track the history to find that this volunteer had a malaria infection ten years ago. So they considered this as not a real induced malaria in this case because they cannot find parasites in the other smears.

The two-weeks-old did not show any infection from the liquid plasma. So, based on this study, it pretty much confirms frozen plasma is not likely to transmit the malaria parasite. The liquid plasma, one-day-old liquid plasma, would support malaria parasites growth.

At this point, I also want to mention, just like I mentioned, some of the earliest reviews point out--such as, in 1965, Russia, the Former USSR, published a collection of transfusion-transmitted malaria. They found out, out of 47 patients, 42 were transfused with whole blood--42 were

due to transfusion of whole blood, five were due to transfusion of liquid plasma. Three of them, they found out the plasma had been about three days old.

So, in other words, liquid plasma could support the parasite, at least up to three days.

[Slide.]

So now we have to talk about the concern about the potential viability of the malaria parasite in plasma. When we look further into the frozen plasma area, we have to consider the previous experience drawn in the 1930s and 1940s when they tried to look at the parasite in the frozen state.

Two points I would raise. One is, intra-erythrocytic malaria parasites are known to survive for extended periods of time under varying storage conditions including -78 to -190 degrees. For this part, we have to look at the effect of the freezing and thawing process.

The freezing and thawing, in general, the damage of the malaria parasite to the host red cell is due to the rate of the freezing and thawing process. I think in the late 30's, Caggeshall, Rockefeller and Saunders in Washington University in St. Louis did a series of studies just using citrated blood or heparinized blood. Those are collected from active malaria patients.

They go through different ways of freezing and

thawing. They found out the best way is to do a rapid freezing, a rapid thawing and then the malaria parasite will still be viable because they could prove, by inoculating the thawed blood into another volunteer, it could induce malaria in those volunteers.

Those studies did not involve any anticoagulants, but I wanted to point out that we know dextrose is commonly found in many anticoagulants could further enhance this viable red blood cell and the parasite under freezing temperature. This you can also find in many of the studies done in the mid-1900s.

[Slide.]

This table I show on this slide, I actually extracted out of a chapter written by Dr. Nguyen-Dihn of CDC in the textbook named Malaria published in 1988. It pretty much summarized all the human malaria species you could look at. There is no preservative added. There is no glycerol. No other cryopreservative has been added to this parasite or this infected red cell. Those are stored between -70 degrees and -80 degrees.

You can see that falciparum, vivax--I am using the abbreviation form--and malariae and ovale pretty much could survive for a long period of time under these conditions and still be infective to the human volunteer. All this has been supported by inoculation into new recipients.

[Slide.]

The other concern I think we should look at, at least from our perspective, is when we receive the petition for variance, when we learned this was going to be fresh frozen plasma, we went back to talk to several apheresis or plasmapheresis equipment manufacturers. We gathered some of the data from them about residual red blood cells in the plasma.

Gambro BCT and Haemonetics reported residual red blood cell levels below the detection limit of automated cell counters. Unfortunately, those cell counters have lower limits on the linearity of less than 0.1 times 10^6 per microliter. I know when I talked to people in those two companies, they generally indicated that red blood cell contamination is usually low coming out from this equipment.

But since the criteria is using the automated cell counter, with such a high limit--because, if you translate that, the lower limit would be like 0.1 times 10^9 per ml, per cc of blood. That is quite a bit of red blood cells present in the plasma.

Even from the best data we received from Baxter/Fenwal which they reported in Transplant, actually at the AABB meeting as an abstract, they reported about 40 red blood cells per microliter. If you calculate it, it would be roughly about two times 10^7 per 500 ml of plasma. This

is using Autopheresis C. It is exactly the same equipment Dr. Gorlin is proposing.

When we look at this one, you have to consider all the factors involved of the viability--which may affect the viability of the parasite in the plasma product. I point out to you, freezing and thawing, it depends on how you do it and you would affect some of the more mature parasites.

But I also need to indicate that a human malaria parasite like Plasmodium falciparum is known to sequester in the circulation. So you are only seeing the ring-stage parasite, or a more mature gametocyte in the circulation. The other three do not have this phenomenon but, obviously, when you draw blood from a patient who already has been exposed to Plasmodium falciparum, you are going to see a lot of the ring-stage parasite in the collection.

But the other factor I also need to point out is all different human malaria infections, we are talking about average parasitemia, or the parasite is low in the circulation. It has quite a big range here. Falciparum could go as high as 5 percent in--I shouldn't use the normal malaria patient but, anyway, in the malaria patient has been reported and some as high as--could reach about 15 percent.

Falciparum usually ranges about 0.5 to 5 percent in active malaria patients. Vivax, in general, you will see an average of about 0.5 percent parasitemia. Malariae and

ovale, probably may be lower by a factor of two or three.

No matter how you look at it, if you have an active malaria patient walk into a blood bank donating blood, you should be concerned about the parasitemia there. I know Dr. Gorlin has mentioned about this petition is mainly concentrated on the traveler. We know most people from North America probably would not tolerate too well any active malaria infection. But I am just presenting what I have seen in the literature for you to consider.

In summary, frozen plasma collected from donors with active malaria based on Lozner and Newhouser's study in 1940 did not induce malaria in the recipient. The viability of the malaria parasite could be preserved in whole blood in the frozen state which we have a large body of data to support. Plasma, indeed, contains a significant number of residual red blood cells.

Thank you

DR. NELSON: Thank you, Dr. Syin.

Comments or questions anybody?

DR. FITZPATRICK: Dr. Syin, in the literature, did you find anything on the viability of the parasites stored at -20, since that is what most of the plasma is stored at?

DR. SYIN: The study conducted by Lozner and Newhouser is stored under -20 degrees. They freeze in alcohol and dries and is stored at -20 degrees. But I have

to go back to one other study I think conducted in the '50s, I believe. They looked at the red blood cells, by themselves, stored under -10 degrees. They claim that they only suffered maybe up to a 20 percent loss of the red cells.

As you probably know, malaria parasite survival pretty much mimics the storage condition of red blood cells. So I would speculate the parasite probably could be still viable there.

DR. NELSON: You cited Dr. Bruce-Chwatt saying that plasma transfusion did not, in his opinion--

DR. SYIN: No, he just says there is never a single case reported.

DR. NELSON: I just wondered if he cited any data other than his pontifical opinion.

DR. SYIN: No, but I think this is reminiscent of what we see in people citing Wells and Ala's paper because we are actually seeing--I have done this search. Prior to 1985, before they published, there is not a single reference mentioned about cryoprecipitate being implicated. But, since 1985, everybody mentions cryoprecipitate, citing Wells and Ala's paper. That was very critical for me to track down the original author.

But, unfortunately, they never published it and they said they drew on personal experience. I cannot argue

against it because, just like you mentioned, Dr. Bruce-Chwatt also mentions transfusion-transmitted malaria usually worldwide has been underreported because he cites several studies, especially in France, the study in 1970. Actually, they could see in the literature and what is serving the blood bank actually has showed up, like, 50 versus 100 cases.

DR. EPSTEIN: Chang, I have to say I ended up confused. I thought I had it straight, but you seem to have told us a couple of things, first of all, that it can be shown that viable malariads can survive freezing and thawing.

DR. SYIN: Yes.

DR. EPSTEIN: As can some red cells remain intact.

DR. SYIN: Yes.

DR. EPSTEIN: Prior to that, you showed us that the 1943 study with human volunteers appeared to show transmission by liquid-stored plasma but never the frozen plasma.

DR. SYIN: That's right.

DR. EPSTEIN: However, when you reviewed the viability studies, and correct me if I am wrong, you stated that infectivity was shown in the human volunteers so that the frozen thawed products that had viable malariads were, in fact, infectious as transfusion products.

DR. SYIN: This is only in the whole blood. You have to understand, those studies were done because, in the '30's and '40's, those physicians practiced malaria therapy on the neurosyphilis patients. They had difficulty to maintain or induce--I mean, sporozoite-induced malaria. So they are trying to find a method to have a way to keep the preserved malaria parasite in a quantifiable fashion they could use to induce malaria in neurosyphilis patients.

So all the studies were conducted in whole blood and not in the plasma. So I think you have to separate. The only study we see using the frozen plasma to inoculate into volunteers is the 1943 paper by Lozner and Newhouser.

DR. EPSTEIN: That study involved a soft spin, right?

DR. SYIN: Yes, I show it is 2500 RPM for one hour.

DR. EPSTEIN: The other point of contrast was that you stated that the whole blood did not involve preservative.

DR. SYIN: Yes, all those studies conducted in the '30's and '40's, I went back to look very hard. They only mention citrated blood. Some of the articles, they actually mentioned they are only putting in--the mix was 4 percent sodium citrate. So I take it that that doesn't involve any dextrose or any glycerol because I think I have to recognize

any blood mixed in with glycerol could last for a long, long time.

I think Bill Collins, of CDC, just this month published a paper using some of the glycerinated blood to inoculate monkeys. That blood has been preserved for over nine years and they could easily induce malaria in those monkeys. Those are mixing with glycerol.

The table I presented, in the original publication, not a single one mentioned anything about glycerol or dextrose. So, in other words, we need to recognize the fact they are only using anticoagulants like citrate or heparin.

DR. SCHMIDT: Jay, I think you used terminology most people would be unfamiliar with. This was definitely what we would call a hard spin, 2500 for an hour, the soft spin being to make platelet plasma.

DR. EPSTEIN: What I was trying to get at was whether that was a more rigorous spin than would be commonly used to make FFP.

DR. SCHMIDT: I think it was.

DR. EPSTEIN: I think this is more rigorous.

DR. SCHMIDT: Yes.

DR. EPSTEIN: So can we be comfortable with a negative result if, presumably, there was more effective removal of particulates including intact red cells than

would be the current practice in making FFP. I'm sorry, I did use the wrong word, but that is exactly what I was trying to get at.

DR. STRONCEK: Before you leave, I know you alluded to studies on cryopreserving malaria parasites. When people do culture work with malaria for research, how do they store it? Do they use cryopreservatives or do they just freeze red cells?

DR. SYIN: Yes, we are usually using glycerol to preserve the red cells, to preserve those seeded parasites. Most of the time, we preserve the ring stage malaria parasite within the red blood cell.

DR. NELSON: Thank you.

The next presentation is Dr. Monica Parise from CDC.

Monica Parise, M.D.

DR. PARISE: Good morning.

[Slide.]

This morning I am going to talk about malaria, transfusion-transmitted malaria in the U.S. with mainly a focus on fresh frozen plasma as far as what we know about our transmission from that component.

[Slide.]

First, I am going to give a little bit of background on malaria in general and then transfusion-

transmitted malaria specifically. I will given then some information on the epidemiology of transfusion-transmitted malaria in the U.S., especially as relevant to potential transmission from fresh frozen plasma.

I will discuss a lookback we did at outcomes of recipients who received FFP from known malaria-infected donors and then I will close with a discussion of what is known about the risk from plasma from the literature.

[Slide.]

Malaria is a protozoan parasitic disease. It is caused by one of four species of human Plasmodium, which are Plasmodium falciparum, vivax, malariae, and ovale. It is generally transmitted from the bite of an infected female anopheline mosquito.

[Slide.]

It was eradicated in this country in the late 1940s, but each year we have approximately 1,000 to 1,400 reported cases in this country, almost all of them imported infections from U.S. travelers or from foreigners.

A few cases, generally less than 10 a year, are transmitted in the United States, and this includes transfusion-transmitted malaria, which averages 2 to 3 cases a year from organ transplantation and congenital transmission. About once every 1 to 2 years, we have a case or a few cases that are felt to have been acquired through

local mosquito-borne transmission in the United States.

[Slide.]

Of the imported cases that we have each year, about half occur in immigrants, refugees, residents of other countries including people who live in other countries who come to visit the United States, and the other half occur in U.S. travelers, which includes U.S. civilians and military.

A major risk factor for acquisition of malaria in these persons like travelers who live in the United States and go abroad, is a failure to make use of effective malaria chemoprophylaxis, and about 85 percent of these cases are associated with either the failure to take any preventive drug or the use of an ineffective drug or a noncompliant use of either an ineffective or an effective drug.

[Slide.]

I just want to talk briefly about the malaria transmission cycle. Basically, we will start with the mosquito. An infected mosquito injects a form of the parasite that is known as sporozoites that are in its salivary glands, and in feeding on a human and taking a blood meal, it injects those forms into human blood.

They are very brief lived in the blood. In less than 30 minutes, they are taken up by liver parenchymal cells and there they develop in the liver. It takes an average of about a week or two that that developmental stage

called the exoerythrocytic stage in the liver before they reach a stage that are released into the blood.

The liver cell ruptures and releases a form called merozoites into the blood. These rapidly enter red blood cells, they go through stages of development in the red blood cells, and once the parasites mature, the red cell ruptures, releases the parasites, which are taken up by other red blood cells, and thus, another erythrocytic cycle.

That cycle in the red cell is what causes the symptoms of malaria. Its duration averages 36 to 72 hours depending on the species of parasite.

Some of these parasites in the red blood cells go on to another stage of development along the sexual pathway, which produced gametocytes. This is the stage that then can infect another mosquito and propagate the transmission cycle.

The cycle in the mosquito varies. It takes from about 9 to 35 days. It depends on a variety of factors, the most important probably the ambient temperature and humidity, et cetera.

[Slide.]

The four species of malaria parasites do have somewhat differing biologic behavior, and one of the major differences is whether there is a liver stage. Two species do not have a persistent liver stage, and they are non-

relapsing species.

Those are Plasmodium malariae, and although it doesn't persist in the liver, it can persist in the blood for very long periods of time at very low levels, not causing symptoms for many years and even decades in both persons with and without immunity to malaria.

In the current donor exclusion criteria, here and in many other countries, we will never prevent all the cases of this particular species.

The other non-relapsing species is Plasmodium falciparum, and most symptomatic cases from this parasite come up within a few months of travel. Persons who have lived in malaria endemic areas for prolonged periods of time can develop a partial immunity, and they have been noted to have parasitemia, which can be asymptomatic for periods beyond a few months, although rarely beyond one to two years after leaving a malarious area.

This is a species that is responsible for almost all the deaths that occur both in this country and globally due to malaria.

There are two species that do have a dormant liver stage that can cause relapse. They are Plasmodium vivax and ovale. Even without treatment, the liver stage rarely lasts for longer than three years.

[Slide.]

Moving on to transfusion-transmitted malaria, it is rare in the United States, occurring in an estimated incidence of about 1 case per 4 million units collected. It has been associated with a high case fatality rate, probably due to both the compromised nature of transfusion recipients and often a delay in malaria diagnosis after transfusion.

There were 3 cases of transfusion-transmitted malaria reported to CDC from 1996 to 1998, and all were complicated Plasmodium falciparum infections, 2 of which were fatal.

Concern over these 3 cases led us to try to look more closely into the epidemiology of transfusion-transmitted malaria in the U.S., and I will give a little bit of information on that investigation, especially as it pertains to transmission from plasma.

There has been 1 non-fatal case of Plasmodium falciparum since then in 2000, but the work-up is still in progress and we don't have an implicated donor as of yet.

[Slide.]

1963 was really the first year we could get what we felt was adequate, well, at least somewhat adequate information about implicated donors, so we started there and looked from 1963 to 1999, and there were 93 cases of transfusion-transmitted malaria that were reported to CDC during those years.

Let me just say the information we got on many of these, especially the older cases, were from malaria--we publish annual malaria surveillance summaries in the United States, and any cases that are felt to be transmitted in the U.S., there is more detail on than the imported cases, which generally consists of one to three paragraphs of more detailed epidemiologic and clinical information. So, much of the information came from a lookback at records.

In 70 cases where the implicated blood component could be discerned, whole blood was implicated in 63 percent, packed cells in 31 percent, and platelets in 6 percent. So, in this series, plasma was not implicated in any cases.

We were able to implicate an infective donor in 67 cases, and we also found that the incidence of transfusion-transmitted malaria in this country has decreased since the sixties and seventies, and has remained at a stable low level for the last 15 years.

[Slide.]

In preparing for this presentation, the other thing we did was go back to this data set on the cases of transfusion-transmitted malaria reported just to make sure we weren't missing anything, to see if any evidence existed for transmission from fresh frozen plasma in the unsolved cases where we weren't able to implicate an infective donor.

So, we first looked at how many case-patients were reported in that series to have received FFP. That, we were able to find in 10 of 92 cases where there was available information on yes/no plasma was transfused or not.

In 6 of the 10 cases where plasma we knew was transfused, there was an implicated donor identified. In 5 of them, the implicated product was whole blood or packed cells. In the other 1, the implicated component was not mentioned. The patient had received packed cells, platelets, and plasma, but we didn't know, the records did not state what was the implicated infective component.

[Slide.]

What about the other 4 cases where there wasn't an implicated donor? Well, in looking at these, there was 1 case that had received both packed cells and FFP. Both of the red cell donors were serologically negative, which is the main way we initially screen these donors, but had traveled, the records didn't indicate where, it was implied to a malarious area, we don't know, and the FFP donors couldn't be tracked down.

In another case, packed cells, whole blood, and FFP were all received, were all transfused. All the donors tested negative, but one donor had traveled to Ghana. It was unknown which component that donor donated.

In the other two remaining cases, the

investigation was incomplete, even all the whole blood donors couldn't be tracked down.

So, I think the bottom line here is that in this extra look, we didn't find any cases where evidence for transmission from the other components was definitively ruled out that would lead you to think could there have been from plasma.

[Slide.]

The other thing that we were asked by FDA to look at was to look back at recipients of fresh frozen plasma from known malaria-infected donors, just to ensure we had not missed anything.

When I say this, it was not an intentional transmission, but transfusion-transmitted malaria occurs because something has gone wrong, usually in the screening process, and a case slips through. Sometimes the plasma component may get transfused before that case is reported or known.

We felt that it was unlikely we were going to find this because it hadn't been reported to us through our system, but we went back and specifically asked. It is a small number, and it will not rule out possibly the possibility, but especially a positive result that we had not heard about would be very important to know.

So, we contacted blood banks where an implicated

donor has malaria starting in 1990 up to 2000 to ask if any fresh frozen plasma from the known infected donor had gone to a recipient, and if any had been, we asked that the chart of that recipient be reviewed and also review any other records that the blood bank may have related to follow up of that recipient to look for the diagnosis of malaria or an unexplained fever that could potentially be malaria.

There were 14 cases of transfusion-transmitted malaria reported from 1990 to 2000, as I said, one investigation still in process. Of the remaining 13, in 4 cases, no FFP was transfused. It was either destroyed or had been sent for further manufacturing.

In 3 cases, it was transfused without evidence of malaria in the recipient. One recipient did not live long enough to have developed transfusion-transmitted malaria based on the range of incubation periods for transfusion-transmitted malaria in general that have been reported in the literature for the various species.

In 6 cases, the investigation is still pending. Either it has been very difficult to find these charts or we are waiting for review of the chart, et cetera.

[Slide.]

Finally, is there evidence in the literature for or against risk of transfusion by plasma? This mentions a little bit what was mentioned in the previous presentation.

Bruce-Chwatt had compiled cases that again were felt to be clearly under-reported, that were reported to the World Health Organization from 1911 to 1972.

Of about 2,000 reported cases, there is no mention on infection associated with plasma.

[Slide.]

I think you have heard about this study again in the last presentation, and just to recap, there was in the study by Lozner and Newhouser, there was no transmission seen from frozen or dried plasma.

In looking at liquid plasma that was stored for one day, there was 1 definite and 1 that was felt to be a probable transmission, and that had been stored for a week. There was 1 transmission which was felt to be doubtful.

So, I will stop there. Thank you.

DR. NELSON: Thank you, Dr. Parise.

Questions? Yes.

DR. STUVER: How complete is the reporting of malaria to the CDC, do you feel?

DR. PARISE: That is a good question. There have been some estimates down to try to look at the sensitivity of the surveillance system for overall malaria. It has varied. We think maybe on average, 50 percent. Some sites we have looked at have been as high as 70 percent, some as low as 30 percent. There haven't been a lot of studies

looking at it.

There is actually two surveillance systems in this country for malaria reporting. At CDC, we know that our system, which collects much more detailed information on travel and chemoprophylaxis, actually probably picks up less than an electronic reporting system. We are trying to integrate these two systems in a capture/recapture analysis done.

As far as transfusion-transmitted malaria, we think it is pretty good. We didn't find, for example, in this big investigation we looked at anything that was in the literature that we hadn't picked up.

We do think we tend to hear about the unusual things. We think we hear about, for example, if there is a case of malaria in somebody without risk factors that got mosquito-borne transmission, that we generally hear about it.

DR. NELSON: I have a question about the lookback of people who got transfused from a malaria donor. Were these donors parasitemic at the time of donation, or were these people who had a recent history of untreated or malaria, was it known that they actually were parasitemic?

DR. PARISE: Basically, there is very little information of what happens at the exact moment of the transfusion, because usually what happens is there is a

delay after a transfusion that the person gets malaria, then, there is a delay in the time it gets transmitted, and then it takes a while to get all the donors, the implicated. So, you end up usually screening these donors.

Unless you are lucky enough to have a segment from the bag, you are screening them a couple months later, and you do a blood smear, and in those cases, actually, the blood smear only picks up about a third of the patients who are parasitemic, but we don't know at the moment.

We have had some cases that have actually, when we were able to do PCR and test it, that we have picked it up by PCR, and not by a blood smear.

I can look at the data set, I don't have it right in front of me. Most of them are actually from travel, and not from having a history of malaria, but again that gets a little bit difficult because in most recent years, a lot of the cases have been in immigrants.

The majority of those have been from sub-Saharan Africa, and many of those people haven't had a symptomatic malaria infection since they were a child, so it is difficult to remember, I think.

DR. STRONCEK: On your 93 cases you reported, there was none attributable to fresh frozen plasma, but it sounds like from your lookbacks that the people really aren't looking that close for FFP as a source of malaria,

and then the question I have is, in 6 percent of the cases, platelets were implicated, did anyone break that down into whole blood platelets, which have more red cells versus apheresis platelets, which are relatively free of red cells?

DR. PARISE: Let me answer the second one first. That, I didn't do. I am not sure that level of detail would be in the summaries. It is a small number of cases, and if they were more recent, we could look at that just by trying to figure out what the blood bank was and calling them.

My understanding, and there are people here that work in the blood collection in FDA that probably know more about this than I do, but I believe that once there is a case reported, many blood banks would not transfuse anything from those donors until--well, one, until we find an implicated donor, so there is a whole range of donors that could be potentially implicated at the beginning.

So, there would be sort of a cutoff to try to not transfuse them. I think in the cases that did get transfused, what may have happened is that because of this delay in the report, those products got transfused before anybody knew that there was a problem.

This was very difficult. I mean it was hard to track down. In the ones where the investigation is still pending, since some of these had happened over 10 years ago, it was hard to find charts, many of the recipients had died.

One case had been closed for litigation, and the records could not be located, so it was difficult to get a lot of information from this.

DR. LINDEN: Is it known how many organisms are necessary to transmit the disease?

DR. PARISE: It is felt not to need very many. It is felt that about 10 organisms of Plasmodium vivax from some of these earlier studies that have been done can pass on malaria. We know it can happen from needlestick.

DR. SCHMIDT: Would you comment on this question of the P. malariae where there is a persistent for decades, as you say, it may be 30 years, how does that jibe with this proposed guidance of 3 years that you were talking about, Jay?

DR. EPSTEIN: That issue has been debated many times. We know that the history exclusion is not 100 percent. It is estimated that it is at least 98 percent effective. The converse question of would there be a net benefit if you excluded lifetime for history of malaria and/or history of origin from a malarious area, such as five years exposure in childhood, and, you know, basically, the arguments have been that the risk and benefit don't warrant lifetime exclusions and that if you are going to have a temporary exclusion, three years is about optimal.

So, that is just where we have sorted out in prior

discussions, and I wouldn't claim it is perfect.

DR. PARISE: If you look in the U.S., at the number of cases that are reported that come up over three years in people that could potentially be semi-immune people, who used to live in malarious areas, 0.2 percent actually come up after three years.

DR. SCHMIDT: Could you tell us, were all of these cases as far as tested of the transfusion-transmitted, were they falciparum, do we know that?

DR. PARISE: No, they are not falciparum. Really, all the species are represented. When we went back to try to see what happened, according to which donors had met donor suitability criteria, but still, you know, they were out of a malarious area over three years, but something still came up versus those that came up, the traveled, say, within a year or within the criteria, the species distribution differ there.

In the ones that came up when everything went right, but still came up, as would be expected, P. malariae is the most frequent species. In the other ones, I don't have the chart here, but both P. falciparum and vivax are more frequent.

DR. HALEY: Mr. Chairman, I can comment on the three cases, two of which were fatal. Those were former residents of Africa who had revisited Africa within the last

year and were semi-immune, so they were not just travelers, they were people who had been previously infected.

DR. NELSON: Apparently a "hurricane" has just invaded this room. This is not only St. Patrick's Day, it is hurricane season, I guess.

We are going to take a break and hope that the "hurricane" goes away.

[Recess.]

DR. NELSON: To continue the discussion, Dr. Jed Gorlin from the Memorial Blood Centers of Minnesota is the next speaker.

Jed B. Gorlin, M.D.

DR. GORLIN: Thank you.

[Slide.]

DR. GORLIN: For those of you who are astute, that is plasmapheresis, my apologies.

[Slide.]

As has been explained by previous speakers, current malarial deferral criteria require that residents of areas not endemic for malaria, i.e., us nice folks from Minnesota, that we get deferred for 12 months if we visit a malarial area. There is a special DOD request for two-year deferral for visiting Korea, but that is peripheral to this issue.

Individuals who are from endemic areas or who have

had malaria are deferred for three years. Our specific variance request applies only to travelers, not those who have had malaria. It is, however, important to address Dr. Heintzelman's concerns on a broader perspective because the 1994 guidance document is inconsistent with the CFR. So, it is worthwhile to consider the larger question.

[Slide.]

The genesis of this variance request was the observation that Memorial Blood Centers of Minnesota has the dubious distinction of having one of the highest rates of malarial deferral. This is, in part, because Minnesota is a wonderful place to leave in the winter. So, those are essentially travelers to typically Mexico when you go see the ruins.

Donors who are deferred even once for any extended period are less likely to come back. Whether you feel slighted or simply get out of the habit, this is a common observation among blood centers, and it pains us when we have to defer donors.

To retain donors, I entertained a plan to allow us to divert those deferred donors to plasmapheresis, which we perform by an automated collection device that Dr. Chiang Syin has elegantly described.

[Slide.]

We currently have two of these devices which

produce relatively cell-free components, and I give a reference that was documenting the relative leukoreduction, 2 times 10^7 cells does sound like a lot. That is also essentially the cell mass that would be found in 1/250th of a mL of red cells, which is a pretty small spot.

Plasma is currently made, once collected in this device, is rapidly frozen in a blast freezer, that freezes down to -80. It then remains at least -18. Actually, our freezers are -35, but by regulation, at less than -18, awaiting completion of donor testing, which is typically done in one day, but may be longer.

In fact, since we rotate our FFP, like any other blood center, first in, first out. Most FFP is actually in the freezer for quite some time.

[Slide.]

What does the Code of Federal Regulations allow? Well, 21 CFR allows drawing of donors with risk of malaria for source plasma, as Dr. Heintzelman has pointed out, because it gives the exception, "freedom from any disease other than malaria transmissible by blood transfusion."

[Slide.]

What does it not allow, what does it preclude? It is CFR 640.32 specifically precludes this malarial exemption, i.e., it exempts the exemption for donors of plasma or cryoprecipitate.

[Slide.]

Well, that is the CFR. What is the science? I cite again what is probably the fattest textbook of transfusion medicine, Mollison. In that statement, the most recent editions say it is plasma which has been frozen or fractionated has never been known to transmit malaria.

We have heard in elegant detail about the prospective trial in 1943 among volunteer soldiers. I suppose if your choice was getting malaria in an unnamed Army hospital here in D.C. versus being shot at in the Philippines, I know what I would choose, but there were no cases among the 20 recipients of the frozen plasma.

[Slide.]

Dr. Chiang Syin has elegantly described his truly heroic chasing down of this retire Iranian physician, describing in rather elegant detail the single anecdotal case of a lung resection from an individual, a severe hemophiliac, who got homemade cryo.

Having been a hemophilia clinician for many years, surgery on patients with severe hemophilia prior to the era of available lyophilized concentrates was a challenging episode, and one wonders could this individual have gotten other blood products ordered by the intern at night. One will never know, there are no records. So, suffice it to say, it remains an anecdote.

[Slide.]

But I respectfully submit that CBER, in its wisdom, has done the experiment, and they have done the experiment by their own policy of not requiring recall of the frozen units, to wit: the Office of Compliance at CBER receives about 9,000 post-donation information reports annually from blood centers. The single largest category, many from my own blood center, results from donor travel to endemic areas.

Following such a PDI, only cellular products from prior donations are recalled, i.e., platelets and red cells, but not the frozen plasma.

[Slide.]

Since CBER has never historically required recall of FFP or other frozen components, one needs to pose the question why not. Well, that is because everybody knows, it is well known that FFP and its derivatives don't transmit malaria.

Okay. One therefore makes the calculation that about 1,500 units of plasma from donors who later report malarial travel are not recalled each year.

[Slide.]

In truth, there is greater demand for transfusion of red cells than there is frozen plasma, so not all plasma from whole blood-derived units lands up being transfused

into patients. From our own center, and I think a reasonable figure, about one-third of the plasma units collected land up being transfused, at least that is from my own center.

Hence, one may estimate that about 15,000 experiments have been done without a known case of malarial transmission, and I derive that figure, simply saying 1,500 per year PDI reports times a one-third chance that FFP was actually transfused, and going back to Dr. Parise's 30-plus years of experience of reasonably decent reporting since 1963.

[Slide.]

So, in summary, Memorial Blood Centers of Minnesota requests a variance to allow the drawing of donors by automated plasmapheresis for the purpose of making plasma components.

I point out that the current restrictions in the CFR are inconsistent with the CBER policy of not requiring recall of plasma components.

[Slide.]

There is an overwhelming preponderance of historical data to complement the prospective 1943 study for the safety of this practice, and that a single anecdote using admittedly outmoded manufacturing methods should not preclude the allowance of this variance.

[Slide.]

Finally, I want to raise a unique concept that we have adopted. I hold two hats here. One is my hat as Medical Director of Memorial Blood Centers. The other hat is I am the Chair of the AABB Standards Committee.

On the AABB Standards Committee, we have adopted a policy to when variances are granted, to publicize that these variances are granted through a publication called "Standard Source," and this allows other blood centers or blood collection organizations to learn from the practices of others.

If there is something wrong about our standard, then, it gives us the opportunity to change it. If there is something else that others can gain from this exception, it is I think a worthwhile policy.

With that, I thank Dr. Heintzelman for his patience with my badgering and the committee for their time.

Thank you.

DR. NELSON: Thank you, Dr. Gorlin.

Comments? Questions? Yes.

DR. KOERPER: I am compelled to bring this up because it has been bothering me all morning. I wish to point out that the recipients of the frozen plasma in this article in 1943 were not necessarily volunteers. They were patients on the wards at St. Elizabeth's Hospital, which was

at that time a federal mental hospital. So, I would like to come up with another word to use rather than volunteers. I am not sure that these individuals volunteered to be transfused with this plasma.

DR. STUVER: I just have a couple questions. On your third slide, you said that 0.78 percent of your donors are being deferred for the malarial travel. What is that in absolute numbers of donors?

DR. GORLIN: We have about 85,000 donations a year, so that is something on the order of 7- or 800. We have actually had periods in the past of actually over 1 percent. I took the 0.78 from the most recent figures.

Nationally, it represents a significant--when a donor walks in the door, about 10 percent of them get deferred before donating blood. The largest single category is hematocrit, but high on the list, after that, is malarial travel.

DR. STUVER: Also, do you have any data for the persons who are deferred for this reason, what proportion of them do not ever come back to donate again?

DR. GORLIN: We do not have a good way of tracking that. I wish I did, but we do not have that data.

DR. NELSON: You inferred that the travel history of donors for source plasma would have been the same or equivalent to those who donate whole blood in your

calculations, as I understand it. Is that correct?

DR. GORLIN: I am afraid I wasn't making any comments about source plasma. I was saying that the current CFR requirement allows you to draw source plasma regardless of malarial travel.

DR. NELSON: Yes, but if the donors who donate source plasma have a very low travel history and a very low exclusion, then, the members of exposed people to source plasma may have been significantly different than your 15,000. That is the point I was making.

DR. GORLIN: Oh, I am sorry. Let me clarify. The CBER web site from whence I drew that data is derived from only those from volunteer blood centers, not from source plasma. Both sets of data are available on the CBER web site, but the numbers I was using, the 1,497 was from whole blood volunteer centers, and you are right, the reasons for deferral are quite different.

DR. NELSON: Other comments or questions?

[No response.]

Open Public Hearing

DR. NELSON: The American Association of Blood Banks, Dr. Katz, will you give us your wisdom on this?

DR. KATZ: Yes, I have no wisdom. I wanted to express my condolences to Dr. Gorlin for the meteorologic extremes that have necessitated this request for a variance.

I come from Iowa where it is a lot warmer.

The standards for blood banks and transfusion services promulgated by AABB have permitted essentially what Dr. Gorlin has requested for 30 years, and I do believe that the natural experiment that Dr. Gorlin has described should be considered by the committee.

CFR, however, precludes the practice, but the draft guidance that we are eagerly awaiting in its final form has used the terminology, and I quote, "products devoid of intact red cells," identical to that in the standards, and sounds to be permissive.

We would support a change in FDA policy, so that individual collection facilities would not need to request variances, and allow this to go forward.

In answer to one of the questions, we find at my center the dropout rate after deferrals other than hematocrit deferral of repeat donors, about 50 percent don't come back in a time frame of two to three years, so it is a very substantial loss.

DR. NELSON: Are there other statements? Celso?

DR. BIANCO: Celso Bianco, America's Blood Centers. We support the statement that was made by AABB. I have through surveys of our centers, I have estimated that annually we defer 50,000 donors a year among volunteer blood donors because they traveled to what is considered a

malarial zone.

We are trying to obtain more data, but essentially, most of this travel is to resorts in Mexico and the Caribbean.

I also would like to remind--and I hope that Dr. Parise will confirm that--that the last case of malaria associated with travel to the Western Hemisphere occurred in 1982. Since 1982, all cases of transfusion-associated malaria have been associated with people that came from West Africa or African countries.

DR. PARISE: Actually, this data is in press for publication, and when I went back and reviewed it for the 50th time, I actually found two cases in the eighties and nineties that were in travelers. Previously, I think I have presented that there was one. Both were in U.S. residents. I believe one was a U.S. traveler, and the other was a U.S. traveler who had been a Peace Corps volunteer.

So, these were sort of the non-immunes, so two in the last 20 years. One went to West Africa, and I can't remember where the second one went to.

Open Committee Discussion and Recommendations

DR. NELSON: Now, we would like to discuss and consider the questions. There were several questions that you asked on this, so I would wonder if you would review this.

DR. HEINTZELMAN: One thing I would like to remind you is that when we consider the incidence of malaria, and we look at transfusion-transmitted malaria, be it from the Northern Hemisphere or the Western Hemisphere, Africa, Sub-Sahara, wherever, the fact that there are so few cases could also indicate that our policy is very effective, not that these geographical regions are at lowest risk, but that our policies are very effective, and that when you look at the incidence of malaria not regarding transfusion transmission, but the incidence of malaria as a disease reported in the United States--and I am glad to have Monica here--but I think it is about 1,300, 1,400 cases of malaria in the United States each year.

Monica, are you shaking your head yes for the record?

DR. PARISE: That is right.

DR. HEINTZELMAN: I don't have an exact number, but it is not that there is no malaria, there is plenty of malaria here in the United States that is imported in, and some of it comes as a result of mosquitos on airplanes that get here, and some of it comes from travelers that are people that are residents of the United States, that are immunologically naive that go, another comes from foreign visitors that are diagnosed here.

So, there is plenty of malaria diagnosed in the

United States on an annual basis. I am sure you are all aware that when we have large influxes of foreign populations for whatever political climatic reasons that may bring them in, those numbers will generally go up on a survey basis.

So, questions to the committee.

1. An introduction question. Are the available scientific data sufficient to conclude that it is safe to prepare frozen plasma products for use in transfusion despite a history of malaria risk in the donor, and that applies to when the plasma is prepared by separation from whole blood, when looking at technique for preparation, when the plasma is prepared by autopheresis of any type of equipment, of which Dr. Syin presented a number of manufacturers that had equipment, and specifically, then, when the plasma is prepared by apheresis using the Autopheresis C device--which if I saw the data correctly, may have had reported a lower number of residual red cells than some of the other equipment that is out there, so a machine that in theory might produce fresh frozen plasma with fewer residual red cells.

Is there anything I can do to help?

DR. NELSON: Well, let's discuss these questions, the question and the three subs.

Comments? Yes.

DR. LINDEN: Did we see any data on residual red cells in plasma separated from whole blood?

DR. HEINTZELMAN: Not that I am aware of. Dr. Syin?

DR. SYIN: I have specifically asked the manufacturer about the residual red cell in the plasma through plasmapheresis.

DR. HEINTZELMAN: Not through whole blood. I believe that the intent of the question is that the preparation without a hard spin, as was discussed for some of the earlier studies, it is meant to imply that the residual red count is unknown and with lack of control in this case, so the logical conclusion is that it would probably have a higher residual red cell count than a specific autopheresis technique.

DR. SYIN: Yes, I believe that is the case because I think I went to NIH library to take out '70 or '80 books on plasmapheresis. The number is much, much higher than what is being reported by Baxter. I think Baxter also provided some data with Haemonetics PCS, I think that shows a PCS to have 10-fold higher red cells in their plasma.

DR. NELSON: The data you are discussing related to red cells and merozoites, but gametocytes can be extracellular, and it wouldn't cause symptoms in the recipient, but it might transmission if gametocytes survive.

Do gametocytes survive freezing?

DR. SYIN: No, gametocyte, by definition, is intracellular parasite, and the gametocyte will only transmit it to mosquito, and will not transmit it in human.

DR. NELSON: But those banana type things you see, they are extracellular for Plasmodium falciparum, aren't they?

DR. SYIN: They are intracellular.

DR. NELSON: So, that relates to cells, as well.

DR. SYIN: Yes.

DR. SIMON: As I said to one of the presenters during the break, to you also, that I am very impressed at the extent to which the FDA and CDC have really looked into this issue and gone back into the literature and found out all the information that is available, also, all the clinical information that is available now, and it seems to me, having seen all of this, that at least I am comforted that the variance could be granted and that we could answer yes to the questions.

I think as a practical matter, plasma has not transmitted unless I missed something in the discussion.

DR. HEINTZELMAN: You did not.

DR. SIMON: And the critical--

DR. HEINTZELMAN: You did not, frozen plasma.

DR. SIMON: Frozen plasma--and I think the data,

although I think they have done a very good job of telling us the possibilities here and there that could come up, I am certainly strongly persuaded that the investigations that have been done comfort one that there should be no risk to granting such a variance.

DR. HEINTZELMAN: The Public Health Service in the United States is incredibly fortunate to have at its disposal some places like CDC and NIH and the FDA to seek these kinds of collaborative efforts. So, I believe it is probably unique on the globe.

DR. NELSON: There are actually two questions here, though. The first one is are the data sufficient to conclude it is safe, and then the second one is balancing the risks and impacts on supply, what should be the policy. So, we have two questions to vote on, as I understand.

DR. SIMON: Right. I was speaking specifically of the first, but I would agree with the current FDA policy on the second.

DR. NELSON: One could vote yes or no to either one or both.

DR. McCURDY: If I understand it correctly, we have 25 instances where plasma from known infectious individuals have been given and not transmitted, that is, 20 from the St. Elizabeth's study and 5 in the more recent data from CDC.

I am not enough of a statistician to be able to calculate what the 95 percent confidence limits are of zero out of 25, but I suspect it is probably somewhere between zero and 3 and zero and 5, so that the data are somewhat limited as far as the "n" is concerned.

The other comment that I have about the so-called FDA experiment of releasing all of this plasma is that in this, as well as many other things, gold is where you find it, and unless you are conducting a certain amount of active surveillance or a fair amount of active surveillance, you will miss them.

A postoperative fever is not likely to be attributed to transfusion malaria, particularly fresh frozen plasma, but it is going to be attributed to a number of other things which I think accounts in part for the frequent fatalities, and that the transfusion malaria is not recognized until it gets so bad that it almost is obvious or somebody picks it up on a routine blood smear, which is not routine anymore.

DR. NELSON: I would think that the CDC or somebody might be able to get some more data than the 25, and the study that I think might be useful is people who have received fresh frozen plasma or plasma that was later found that the person had a risk, to track down the recipients and look for serologic evidence in those

recipients of malaria and get a travel history and what have you.

What we don't know is of those 1,500, that most of them have traveled to the Caribbean, and most of them don't have malaria probably, I mean it is mostly travel history. The small number that were reported were people who subsequently developed malaria and probably were infectious at the time of donation, so that the numbers are rather fluid depending on how many exposures there really have been.

DR. McCURDY: Those five came from lookback, and the lookback, as many lookbacks, had its limitations in being able to track down particular recipients.

DR. NELSON: On the other hand, given the infectivity of malaria and the small numbers of organisms that could transmit if they were viable, you know, 25, they are really good negative cases, is in this instance, you know, better, more persuasive than with some other agents, I would think.

DR. SCHMIDT: Something perhaps belonging to the earlier discussion rather than the plasma issue, but my recollection of the reports in the MMWR, I think there have been two like maybe in the last five or six years where they reviewed the transfusion malaria. Most of the very few cases, the donor had given a faulty history, so that you can

write whatever you want, but it still doesn't work. It doesn't really apply to the plasma end of it, but--

DR. HEINTZELMAN: That is one of the reasons why we have, on a side note, been readdressing the malaria guidance document and have had prior presentations with the BPAC, looking at furthering the questions, so that we can try to identify these people and be more clear and what it is we are trying to understand from their travel history, you are correct.

DR. FITZPATRICK: I don't think we can ignore the 93 cases, though, that CDC--the 93 reported cases that they did the lookback on and found on definite implication of a fresh frozen plasma product in those cases.

So, while they have some unresolved cases in there, I think you have to add those to the 25 in the literature because that is 36 years of history of transfusing products that may have had malaria in them.

DR. McCURDY: Actually, I think the 5 cases that I was referring to are the ones from the lookback, and it is my understanding that of the other 88 cases or so, either the fresh frozen plasma was not transfused or, on lookback, they couldn't locate the recipient, so that those 93 cases, I think only 5 are carefully enough worked up so that you can be sure. The others are iffy and dependent upon passive surveillance again.

DR. FITZPATRICK: Monica, it says implicated product. Do you know if they got FFP in any of those other cases?

DR. PARISE: No. When we found an implicated donor and knew the implicated product, none of them got FFP. Basically, on this lookback, there were 13 that we were able to look at. I mean it was hard enough to go back to 1990, I can't go back to the seventies, but there basically, there were only 3 that we were able to look at well, that they could find the records or have finished it, that they knew that they got, you know, it was a malaria-infected donor, they knew somebody got FFP, and there was no evidence of malaria as far as could be determined from the chart.

So, there was only 3 that we could add in there.

DR. McCURDY: That makes it 23, not 25.

DR. SIMON: But I guess the question is, is this an area in which one needs greater numbers or further study, or are we comforted by the totality of the data back to I guess the forties, and that is the argument I was making.

I obviously can't exclude that a postoperative fever here or there might be due to malaria, but there is so much absence of data to implicate the plasma here over many years with some very good efforts made by scientists and presented to us today to look for, that I feel very comforted.

DR. STRONCEK: I agree with Paul, there is only one study, it is the 1943 study and the three donors. The study in 1943, honestly, some of the volumes were small, there was 80 mL's in some of them, so if there is a dose effect, the FFP off whole blood is about 200 to 250 mL's, I am not sure on the Autopheresis C, but it is probably higher, and we don't know what the levels of Plasmodium were in there.

So, to me, it is iffy. If someone were to come up, you know, a student that is working for me, and said is it worth repeating that study, maybe, maybe not, but it is only one study.

DR. NELSON: Comments were made earlier about volunteers, and actually we have learned a great deal about malaria from volunteers using drugs and other things, and I agree that we don't know whether the volunteers were you, you, and you, or whether the volunteers were really volunteers, but nonetheless, a volunteer study I don't think would be out of the question to help answer this question.

DR. McCURDY: Didn't we hear that there are now primate models that could be used, and volunteers are no longer necessary? It wouldn't be too difficult a study to do if one were set up to study malaria in a primate model. I am not quite sure where there might be any support for such a study.

DR. NELSON: I think that the presence of data is somewhat underwhelming, but the absence of data is perhaps somewhat reassuring, but those are different levels of assurance, I think.

DR. MITCHELL: I am still concerned about the--I mean I understand the epidemiological data, that has not shown transmission--but I am still concerned about the theoretical basis, and if we know that malaria can withstand the freezing process, and we know that there are, in fact, red blood cells that are in fresh frozen plasma, it seems that there is a significant number of red blood cells in frozen plasma, then, there is the theoretical risk of this transmitting, and perhaps the reason that it hasn't been transmitted is because of the policies that are currently in place, and that is why I would be hesitant to relax the policies that are currently in place.

DR. FITZPATRICK: But the policy that is currently in place allows us to not recall those products and transfuse them, so the policy that is in place and is being used is while not a controlled study, is what we see reported by CDC, are the results of, as Dr. Gorlin said, decades of a sort of semi-prospective study, which says that this is the policy that is being followed.

There has been no recall of frozen products because we found an error in post-donation information and

have a traveler to a malarial area. So, those products have been in circulation and being transfused.

DR. NELSON: I would like to remind, though, that there are two series of questions. One is are the data adequate, and secondly, should the FDA continue its current policy. I still think one could answer those questions differently.

Maybe we ought to stick with the first question first, or are we ready to vote on this?

DR. McCURDY: It would seem to me that it might be possible and feasible for one or more blood centers, who is affected by this, merely to conduct a lookback on the recipients of plasma that may not have been recalled, whereas, the red cell products were, that is, post-donation information used to conduct a lookback.

DR. NELSON: The current policy doesn't allow--maybe I am wrong--doesn't allow fresh frozen plasma, it allows source plasma, right? So, wouldn't that be more difficult for a lookback?

DR. HEINTZELMAN: I think what you are talking about is that we allow a malarial risk for the collection of source plasma for further manufacture, because we exempt the question about malaria, but we do not do that for what we call our whole blood donor questionnaire.

DR. NELSON: So that the current policy, there

wouldn't be any fresh frozen--no, there would be because the risk came up later. Okay.

DR. KOERPER: And that fresh frozen plasma is already--that is the 1,500 units a year we are talking about. Those are where post-donation, it became known that the donor had traveled to malarious areas. Any cellular components are withdrawn if they haven't been transfused, but the FFP is allowed to be transfused, so that is already happening, so I guess the question is whether anybody could now track the recipients of those units of FFP.

DR. NELSON: Again, it was travel.

DR. KOERPER: Yes, we don't know that the donors were infected.

DR. HEINTZELMAN: Right. That could easily be 1,500 units that had no Plasmodia in them, we just don't know.

DR. NELSON: Jay.

DR. EPSTEIN: I just want to add one more perspective. The question is how good is the, quote, unquote, "FDA experiment," where we have been allowing transfusion of units that were in inventory in the face of post-donation information.

Well, one way of getting at this is to ask, well, what is the likelihood that a traveler to a malarious area has malaria, and what Dr. Parise told us is that there are

about 1,400 cases a year, about half of which are in travelers.

I asked, well, how many travelers are there, and the answer is about 20 million a year. If you assume that the malaria is even 50 percent under-reported, then, the malaria rate in travelers is about 1,400 out or 20 million, or about 1 in 14,000.

If you were to assume that it is at the same rate in people who fail to give travel history, and that is, of course, an unverified assumption, but it would be the worst case, it would imply that there is no selection by history.

Then, the risk of malaria at that level would represent the entire experience estimated by Jed Gorlin for the U.S. blood system, and he estimated that there were 15,000 exposures based on post-donation history. So, if the risk was only 1 in 14,000, and the total experience with units not captured is 15,000, you might never have seen one.

Now, of course, the post-donation information itself may be under-reported, so this could be off by some factor, I don't know what factor, but even if, say, 50 percent of such information is not reported, you are still sort of in the same ballpark where you might not see a case, and, of course, also, you have to factor in that blood recipients may die before their infection is recognized.

So, I am not sure that that information is

compelling. The second point that I would raise is there is a difference in magnitude. If we talk about continuing the current policy, which leaves on the shelf what got on the shelf, compared to a policy that says it is safe to collect units prospectively in the face of travel history to a malarious area, in that case, what we have learned from Celso Bianco is that there would be 50,000 candidate donors a year from whom we could proactively prepare FFP either from whole blood or by apheresis.

That then compares to the current level of what is being said is about 1,500. Now, 1,500, of course, isn't accurate because there is under-reporting, but, you know, even if you said that there was 10-fold under-reporting, which I think would be an overestimate, that is still 15,000 compare to now allowing 50,000.

So, I think just in terms of looking at numbers coming through, in other words, accepted donors, products on the shelf, you are talking about a significant change in the potential risk. In other words, if you believe there is some finite potential risk, then, there is a big difference saying that the units on the shelf are okay, because there are only so many of those, whereas, if we change the policy to accept donation in the face of history, we are really opening the door quantitatively to a multiplier of a potential finite risk.

DR. NELSON: Thanks for summarizing my thinking on this.

DR. STUVER: Also, too, I mean it may be that those persons who identify themselves post-donation as having that history, are different from those who defer themselves in the very beginning with respect to their risk.

DR. McCURDY: One thing that occurred to me, I wonder what the need is for fresh frozen plasma collected in this fashion. It seems to me that with the possible exception of AB fresh frozen plasma, FFP is not in particular short supply. You can always use perhaps a little bit more for fractionation, but I am unaware that there is a dying need for additional need for FFP from blood centers.

DR. NELSON: The other argument is retaining the donor, I guess that is one of the things that was made.

DR. HOLLAND: Paul Holland, Sacramento Blood Center.

I would like to speak to the issue of we are losing donors through a whole variety of mechanisms, some theoretical, some real, and the point was made that about 50 percent of people that are deferred, the actual term is "rejected" in their view, don't come back. I think that may be even an overestimate.

In our center, where we try to recapture and hold

these people as research donors, we can salvage some of them through that period of time, but people who are rejected don't tend to come back. We are already insufficient in blood supply. We import blood from Europe. So, any way, with minimal risk, that we can use these donors and keep them in the system, to get them back to donating whole blood or platelets, I think would be worthwhile.

So, from the perspective of a regional blood center, anything you can do to not unnecessarily waste donors, reject donors, I suggest and I hope that you will do.

Thank you.

DR. CHAMBERLAND: I guess this is a question for Dr. Gorlin. If the variance were to be granted, I guess I was just curious, how it would work and how well you think it would work. Do you have some sense that as people presented themselves for donation and were told their malaria travel history precluded them from donating, that they would be willing to donate through apheresis, and the time to donate through that process versus a routine collection of a unit of blood, is it very different, would you realistically do you think capture some of these people with this alternative?

DR. GORLIN: I think we realistically would. I do not want to overestimate the magnitude of this program. We