U.S. FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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BLOOD DONOR SUITABILITY

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WORKSHOP

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Thursday, December 9, 1999

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The workshop met in Conference Room 1066, FDA Conference Center, 5630 Fishers Lane, Rockville, Maryland, at 8:00 a.m., Jay Epstein, director, Center for Biologics Evaluation and Research, presiding.

PRESENT:

JAY EPSTEIN	CBER
ELIZABETH CALLAGHAN	CBER
JOSEPH WILCZEK	CBER
LARRY FENNER	Session I Moderator
ELLEN LAZARUS	Session II Moderator
TOBY SILVERMAN	Session III Moderator
LINDA CHAMBERS	Speaker
JOHN FORREST	Speaker
JED GROLIN	Speaker
N. REBECCA HALEY	Speaker

PRESENT (Continued):

DALE MALLOY	Speaker
BRUCE NEWMAN	Speaker
STEPHANIE NORRELL	Speaker
LINDA PAPENFUS	Speaker
RICHARD ROBINSON	Speaker
MERLYN SAYERS	Speaker
TOBY SIMON	Speaker

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(8:08 a.m.)

MS. CALLAGHAN: Good morning, everybody. I guess we'd better start before we run over time.

I'm Elizabeth Callaghan, and I work in the Office of Compliance and Biologics Quality, and I'd like to welcome you all here to the third donor suitability workshop that FDA has presented.

I think we have some very interesting and controversial subjects to discuss, and I'm sure there are going to be many differing opinions on the issues that are being presented. It should be very interesting to hear what our speakers have to say.

Before I start, we'll get a few of the housekeeping chores out of the way. The restrooms are directly outside the door, and there are vending machines in a little room right outside the door for coffee breaks.

Also phones. Do we have any phones, Joe?

PARTICIPANT: Yeah, there's a phone for emergency phone calls right outside the door where you checked in.

MS. CALLAGHAN: Okay. Joe has just informed me that there's a phone right outside the door for emergency phone calls.

In your packet should be a list of nearby restaurants to go to during the lunch break, and I guess there is not too much else other than to get this show on the road.

So without further ado, I'd like to introduce Dr. Jay Epstein, who is the Director of the Office of Blood Research and Review who will open the program.

And, by the way, please fill out your evaluations at the end of the show. That should also be in your packet.

DR. EPSTEIN: Thank you, Elizabeth.

And good morning, everyone. Let me particularly commend you for finding this new location for conferencing. It's quite a nice environment, but I think after the challenge of locating it the rest of the workshop will be easy.

It's my pleasure to add a word of welcome and to try to frame for you what we're about this morning, if I could have the next slide.

As Elizabeth Callaghan said, this is the third of a series of public scientific workshops related to suitability criteria for blood donors. The other workshops were those held November 23rd, 1998, when we discussed issues concerning deferral related to

high risk behavior, and that is an ongoing discussion that FDA is having.

And then on July 21st of this year, we held a workshop concerning the deferral of donors based on a history of hepatitis.

And these scientific workshops are intended to assist the FDA in framing its current thinking on issues related to donor suitability, and they are, indeed, a prelude to rulemaking which we have announced that we're doing as part of updating regulations in the blood action plan, about which there has been public presentation.

And those of you who are unfamiliar can find that described on CBER's Web site.

Let me also mention that there's a parallel initiative going on to define criteria for donor suitability in relation to human cellular and tissue products, including reproductive tissues. In September '99, FDA published a proposed rule on communicable disease controls pertinent to human cell and tissue derived products.

And there is, if you will, an over arching effort in cooperation with the CDC to reexamine comprehensively the scientific underpinning of the current standards that are applied to donor screening

and donor testing.

Next, please.

In the next couple of slides I'm going to summarize for you some of the publications that have come forward by way of rulemaking and guidance related to blood standards.

Most recently, in August 19th, 1999, FDA published a set of policy documents including an announcement of proposed rulemaking, advanced notice of proposed rulemaking relating to tracking and notification of particularly plasma derivative recipients targeted toward people who receive their product at home and may need to be informed about recalls and withdrawals sort of directly from the manufacturer to the end user level.

Then we published a direct final rule regarding revised requirements for blood and components. We have now already finalized the direct final rule on plasma derivative standards. That rule was published May 1999, and based on analysis of comments received, we will decide whether we either do or don't have to continue the rulemaking process for the blood component standards.

The way it works is if you publish a rule as direct final, it becomes automatically finalized

unless there are significant adverse comments.

Additionally, we published a proposed rule on requirements for notification of a deferred donor, and we published the proposed rule updating the donor testing requirement, particularly to include testing for Hepatitis C and for HTLV.

Let me just remark that these policy documents were the subject of an open public meeting that was held on November 22nd, just last month, and in conjunction with the announcement of the public meeting, we did extend the comment period on those documents to December 22nd. So it's not too late if, indeed, this is the first time you're hearing about it.

Now, let me just quickly summarize on the next two slides some of the other policy documents that have been brought forward, and these are in backwards in time chronological order.

We have very recently published a draft approvals policy for nucleic acid tests, and this, of course, is subject of great interest to blood bankers because these products are in widespread use under investigational exemptions, and we look forward to moving quickly through the licensure process once applications are filed.

Additionally, we have just again published

revisions to the precautionary measures to be taken for prevention or reduction of the theoretical risk of transmission of CJD and new variant CJD. Again, that came out just recently in November.

We last published draft updated guidance on HCV look-back in June 1999, and I know that there is a lot of expectation that we will now come forward with the final guidance, and we're hoping to do that fairly soon.

We recently published in May guidance on standards for testing of platelets and platelet substitutes, efficacy standards to assist sponsors with clinical trials for fibrin sealants.

Next please.

We also, as you know, have the biologics licensing initiative which has eliminated the establishment license and substituted a single license application based on product. It does a cross-containment establishment section.

And in conjunction with that new application format, all of the biologic products have had new guidance issued so that sponsors know how to file the application. Therefore, we issued guidance, and these are now all final guidance, which means, of course, intended for implementation. All guidance is

nonbinding on the industry and the agency. It's an expression of FDA's current thinking and expectations, and FDA will consider alternative procedures.

Nonetheless, when we say that a guidance is final, we mean that it's our expectation that it will be used unless rationale is given for an alternative.

Anyway, so we filed -- I'm sorry. We published the final guidance for the clinical manufacturing and control section of the biologics license application applicable to blood products for blood components, related in vitro diagnostics, and also plasma derivatives, all in the last year.

We also are developing a pilot of monograph type standards which will be moved into the CFR and which will be used as a basis for licensing based on certification of compliance rather than a detailed validating submission, and the first such pilot program is for gamma irradiated blood components, and again, guidance for implementation was published in January 1999.

We've published a draft -- it shouldn't be "daft." It's "draft" -- guidance on uniform labeling, November '98, and we published the standards for HIV-1 nucleic acid tests in July 1998. I think that actually should be draft, and I believe that the final version

is, again, moving very quickly through the system. And that's more or less the kind of document we used to call a points to consider.

So this is by way of background to give you a feeling for what the agency is doing in the large. We have a very broad, sweeping initiative that was started in July of 1998. It has a number of dimensions.

One central dimension is updating all of the regs. and guidance, and I think that this summary shows you that we've been extremely active in delivering that commitment.

Now, what I would like to turn to is framing the issues for today's workshop. Basically -- next slide, please -- we will be talking about three subjects related to suitability standards for blood donation. These concerns donor deferral registries and how they are utilized, standards for donor weight and product volume, and the question of FDA standards for deferral based on history of cancer.

With respect to use of donor deferral registries, we are hoping that we will have a detailed discussion of three pivotal issues.

First of all, where in the collection process should the donor deferral registry be reviewed?

And the question in a nutshell is: do you have to check the registry before you do the collection or is it okay to wait till afterward?

And what the FDA is seeking is input on the feasibility and utility of a requirement that we might promulgate that the registry should be checked first so that the collection does not occur.

Now, this is an echo. Those of you who have been in this business a few years will remember that we brought this issue to a Blood Products Advisory Committee several years ago, and we were told that the technologies to facilitate this were emerging, and that if we just waited about two years, we could indeed make this a standard, but that it was desirable.

So we're revisiting that issue definitely with an eye toward considering the up front checking as a requirement.

Should donor deferral registries be shared? Well, the question here is, you know, shared how widely. Shared nationally? That would be one extreme. Shared only in that they're accessible at the site of collection? That would be the other extreme, or perhaps something in between, which is that within the facilities of a single licensed establishment the record should be shared.

And of course, when you're talking about shared records, you also have to be talking about how often you expect them to be updated because not all systems will necessarily be on line. Of course, that's nice if they can be on line, but there is the notion that there may be some periodicity to updating and should there be a regulatory standard if we go that route.

Next please.

So the second set of issues concerns donor weight and collection volumes. There have been again previous advisory committee discussions about donor weight. Most of the issue has focused on the low weight donor, and we do realize that the health considerations vary with underlying determinants related to race, related to habitus and stature.

But the linkage to collection volume is the sticky wicket. There's the question of what is a safe volume to collect, and should we have nomograms for blood volume related to weight? How should we label low volume collections? If we have prohibitions on low donor weight, to what extent will that compromise the availability of blood? That is to say what percent of the donor pool would be excluded.

And if, in reverse, we permit low weight

collections on some sliding scale related to donor weight, perhaps also factoring in nomograms related to, you know, body surface, et cetera, which are all surrogates for blood volume, of course, the question then is what should a physician expect.

Is there an expectation for a standard blood unit? And how should that expectation be framed in terms of volume or in terms of hemoglobin content?

So that's the set of scientific issues related to donor weight and volume, and again, remember where we're heading is to try to figure out if there should be a regulatory standard in the regs.

And lastly, last slide, please. We would like to discuss today the question of deferral of donors based on a history of cancer. Currently the FDA does not have a policy on this, although the AABB does, and the question is: should there be? And if so, how should the deferral be frame? Is it all cancer? Should there be exceptions? Should there be automatic or algorithm driven reentry criteria based on treatment and presumed cure?

And really this is the form frust (phonetic) of a whole set of policy questions which lie down the road regarding conditions that are of medical concern where transmissibility by blood products is

unproven and where in most cases the conditions have unknown etiology

And, once again, the issue for the regulator is whether we should standardize donor suitability criteria in the face of those unknown, but presumably on the basis of some consensus view of precautions that are reasonable based on the current science.

So these questions, of course, will be reiterated as the sessions, the discussion sessions are framed by the moderator.

So what I'd like to do at this point is turn the podium over to Larry Fenner who will be the moderator for the first session.

Thank you very much, and I hope we all enjoy a very productive day. Again, I appreciate all of you making the effort to come assist us and, of course, indirectly yourselves, with this policy initiative.

DR. FENNER: Well, as Dr. Epstein mentioned, there's going to be a reiteration of the topics that he talked about, and he touched on everything that I was going to say. So I can make this real short and sweet, I believe. But I'm going to present FDA's position on the use of donor deferral

registries.

Currently FDA has two regulations that address the use of donor deferral registries. The first one is 21 CFR 6061.60(b)(1)(ii), which says that records shall be maintained that include permanent and temporary deferrals for health reasons, including reasons for deferral.

Next.

Also, there's 21 CFR 6061.60(e), which states that a record shall be available from which unsuitable donors may be identified so that products from such individuals will not be distributed.

FDA believes that a revision of 6061.60(e) would result in a safer blood supply.

The first change would relate to a lack of requirement to share donor deferral records within an establishment. Because there's no requirement to share this information, a donor who donates at different locations and doesn't consistently provide the same health history information could be deferred at one location, but not deferred at another location.

Consequently, FDA proposes that all donor deferral records generated at each of an establishment's location should be available at every location under the control of that establishment. This

proposal refers only to the deferral records that are generated within an establishment, and we wouldn't expect you to be sharing your deferral records with competitors.

A second change relating to 6061.60(e) would address the requirement for the review of deferral records only to prevent the distribution of blood products rather than the collection. Because of this, the way the regulation is written now, blood can be collected prior to the determination of a donor's deferral status, and therefore, unsuitable products can be collected that may be erroneously released.

Currently blood establishments rely on their quarantine systems to prevent the release of these unsuitable products. However, FDA really doesn't collect the data that would show how many products are collected from deferred donors that eventually have to get disposed, but we do have some error/accident data that come in that show that there are some quarantine related errors and, in fact, relying on the quarantine system may not be the best thing.

The first slide I'm showing here are donor screening errors and accidents, and these are -- donor screening was not performed for some reason. The donor was actually deferred, and the products were made

available for distribution.

The numbers are relatively insignificant compared to the total numbers of errors and accidents, and I don't know if you can see this in the back, but like this is for fiscal year '97, '98, and '99. I have three slides that are going to show this data, but for fiscal year '97, there were 720 donor screening errors out of 11,076 total errors and accidents reported that year.

So out of that, there were 102 that were related to the donor screening not being performed, and the donor was actually previously deferred. In this I have the blood as yellow and the plasma as red.

I realized last night while I was trying to get to sleep that I should have reversed the colors, but it was too late.

(Laughter.)

DR. FENNER: So anyway, in 1997, there were 102 error and accidents reported. In '98, there were 61, and in '99, there were 52. So the numbers are decreasing, but in general, for the last about two years -- I'll throw out '97 because there's been a drastic decrease since then -- but in the last two years, about five to six percent of all errors and accidents related to donor screening, and of these

donor screening errors and accidents, approximately seven percent of them resulted in erroneous release because donor screening wasn't performed. The donor was on the deferral list, and the products were made available for distribution.

The next chart shows the storage and distribution errors that were due to a failure to quarantine due to medical history and this is where the donor came in, gave a medical history that should have deferred them and for some reason they didn't quarantine the product, and it was released.

So, again, the numbers show that there were 118 in '97, 99 errors and accidents in '98, and 72 in '99. Again, the numbers are decreasing.

So between five and nine percent of all errors and accidents for the last three years relate to storage and distribution and between nine and 12 percent of those are due to a failure to quarantine the products, and the donor should have been deferred and he wasn't.

And the last slide shows, again, storage and distribution errors. This is another subcategory, and these are all the inappropriate releases.

There's a change here. It shows that the numbers are actually increasing. It went from 60 to

108 to 148 from fiscal year '97 to '99, and the errors have increased from four to 11 percent in the last three years when compared to all storage and distribution errors. However, the errors related to storage and distribution have declined from 12 to nine percent when compared to all reported errors and accidents.

So finally, FDA's second proposal is that donor deferral records should be reviewed prior to blood collection, prior to and not after, in order to prevent collection of blood products from unsuitable donors.

And that's it. I'd now like to introduce Richard Robinson, who is the Administrator for the American Blood Resources Association's national donor deferral registry and the quality plasma program, and Mr. Robinson is going to be presenting ABRA's experience implementing the national DDR.

MR. ROBINSON: Good morning. My name is Richard Robinson. I am the NDDR Administrator for ABRA.

That title sounds a little bit more technical than it really actually is, but there you are.

I'm going to give you a quick snapshot of

ABRA's national donor deferral registry and how it's used by plasma centers around the United States. First, I'll give you an overview of the system, why it was created and how it benefits plasma centers. Next I'll describe the inquiry side of the NDDR and then the update side. I'll describe some of what I do as the Administrator, and then answer a few frequently asked questions that we get at ABRA, and if time allows, I'll answer questions or I guess we'll be on a panel later.

Next slide, please.

Fortunately a lot of the background of the NDDR overlaps a lot of Mr. Fenner's presentation. As he stated, the regulations do require that blood establishments maintain records of their deferred donors, but it doesn't require them to share them with other companies or blood establishments.

The NDDR is a database that allows plasma centers, all plasma centers who participate regardless of company, to share donor identification information for donors who are permanently deferred for viral market tests. It's designed to supplement CBER's requirement for donor deferral records.

Next, the NDDR was deployed to all plasma centers in late 1993 and contains donor information, donor identification information about donors

permanently deferred for HIV, HBV or HCV viral markers. PCR positive, EIA negative donors are also added to the NDDR, although I think in most instances the PCR testing is done after donors seroconvert. So I don't have any information about how many instances there are of PCR positive, EIA negative donors who have been added to the NDDR.

Along with the thrust of this meeting, it's important to note that the NDDR check is done during donor screening at a plasma center prior to collecting the unit. So if a deferred donor is detected by the NDDR, processing stops at that point.

Next slide.

Here's how the system works. Currently plasma centers check all new donors that they have no previous history on, all new donors who present to donate. Regular repeat donors or qualified donors are not routinely checked because the facility is now building its own donor record file for that particular donor.

The facility calls a toll free number and enters its NDDR center code and password. The donor ID, usually the donor's social security number, is keyed in using the telephone key pad. The NDDR performs a search and returns with the message that

either the donor ID is not found, indicating that the donor has not been previously deferred for a positive viral marker, or that the donor is in the NDDR, indicating that another facility has found this donor positive for one of the three viral markers and has added them to the database.

The NDDR does not make the interpretation to accept or reject the donor. The inquiry ends with a confirmation number of the call and another inquiry could be made following that.

The next slide.

Donor information gets added to the database by the lab or the QA unit, collectively called the central data source. Donors with positive test results are entered into a local batch file on a PC based application no less frequently than once per week, and in most cases daily. The batch file is uploaded to the main database, and the database is appended overnight.

A confirmation report is prepared that confirms the addition of the donor and notifies the lab or notifies the lab that the donor has already been added to the NDDR by another facility.

Again, let me stress that the information that's entered into the NDDR is limited to donor

identification information, that is, the donor number, the donor name, and the donor birth date.

Let me emphasize that no test results or deferral codes are associated with any donor record. The NDDR is strictly a list of donor names and ID numbers.

Next slide.

In my role as Administrator, I perform the following activities. Primarily I run activity reports of monthly usage. I also update user records as new centers want to start using the NDDR or centers close and discontinue their use. I create passwords and center codes for those new centers and deactivate passwords for the centers who discontinue its use, usually because the center is closed.

I can view donor records and respond to questions from facilities about when or where a donor was entered into the NDDR. Again, let me emphasize that I cannot change or delete any donor information in the NDDR. There's only one change that I can make, and that is each donor record has a laboratory or central data source associated with it. That central data source is the only facility that can modify that record to change a birth date, correct a name, or mark that record for deletion.

The only change that I can make is to change the laboratory code associated with that particular record. For instance, if a laboratory merges, is bought by another company, goes out of business, and another company decides to pick up that company and manage that donor's records, then I can change the authorization for the central data source to manage that record.

Next slide.

I thought you might be interested in some numbers about the NDDR usage. There are approximately 400 plasma centers across the U.S. using the NDDR. Each month they perform an average total number of inquiries averaging about 65,000 per month.

Next slide.

Of those 65,000 average inquiries, an average of about 650, or about one percent of those inquiries, result in detecting a donor who has previously been found positive for a viral marker.

Next slide.

Each month about 1,800 new records are added to the NDDR. Currently the NDDR contains just over 210,000 records. Because the NDDR tracks only donor identification, I have no way of knowing how many of those deferrals are applicant donors and how many

are seroconverting qualified donors.

Next.

And now for some frequently asked questions.

How does ABRA insure that all centers add their deferrals to the NDDR? The use of the NDDR is required for QPP certification. So each new plasma center that intends to collect normal source plasma and sell it to a U.S. based fractionater must use the NDDR.

When a facility contacts ABRA to get its center code and password, we verify that the laboratory who does their testing also participates so that their deferred donors will be added to the NDDR.

Next slide.

How are reentry donors handled? I've discovered that the term "reentry" sometimes has different meanings to different people, but for this presentation we'll use the official FDA term.

This question really has limited scope because very few companies, very few plasma companies actually do reentry testing, and the reason is very simple. Reentry testing represents a laboratory expense with no corresponding unit revenue, and since the donor has already been probably a little bit made angry by being on the deferral list, it's unlikely that

they're going to continue to donate at that particular center.

So our experience has been that there's really very little demand for reentry testing, but if it was done, here's how it would be done. It's up to the laboratory or the central data source to maintain the records of testing for a particular donor, and if a donor is retested for reentry purposes, the laboratory would have those records and then it would be merely a matter of going into the NDDR and sending a message to mark a record for deletion. Of course, those records are not actually deleted. We do have an audit trail for all changes made to a record, but it's marked as deleted so that if someone should make an inquiry on that donor identification, it would indicate that the donor was not found.

There's also a monthly reporting for those donors that are flagged for deletion, and I can verify those deletions with the laboratory.

Next.

We do have some future developments in the works, as well. We're in the process actually of redesigning the whole NDDR with a new software vendor. This new redesign will allow on line inquiry capability and visual confirmation on screen rather

than over a telephone.

We've discovered that along with regional variations in speaking, that there are also regional variations in hearing, and sometimes when you hear a verification code over the telephone what they hear is not actually what the message was. Hopefully our new redesign will reduce that human element.

We may also in the future contemplate expanding the criteria for adding permanent deferral for high risk activity history. Again though, those donors would only be added just on the basis of the donor identification information. There would be no distinction as to the reason for the deferral included in their NDDR record.

That's all I have for now. Thank you.

DR. FENNER: Our next speaker is Stephanie Norrell from the American Red Cross. I should know the name of that place.

(Laughter.)

DR. FENNER: She's Acting Vice President of Manufacturing for ARC Biomedical Services, and she's going to talk about the ARC experience with the implementation of the donor deferral registry at mobile collection sites.

MS. NORRELL: I went with a low tech.

solution for a high tech. discussion.

Okay. Well, good morning, everybody, and thank you, Larry for the introduction and the opportunity speak to this group about our experience with donor deferral at the collection site.

So the very first thing that we had to do when we started down this path was decide what we would call such a process, and the obvious thing to us was to call it pre-check. So this morning I'm talking about pre-check.

I'm going to talk a little bit about what pre-check is and what it is now, how pre-check works, some of the implementation and logistical issues that we went through during our conversion, some statistics that we have on pre-check effectiveness in our organization, and where we're going with pre-check.

So what pre-check is, it consists of using a hand held computer just like this one at our mobile sites. It does not replace any of our existing donor eligibility process steps that we go through. It doesn't make any changes to the blood donation record process that we go through, any of the testing that we do, et cetera. It's an additional measure that we take. And it verifies for us that the donor is eligible to donate the day that they appear to donate.

The search that we use is by the donor's Social Security number, and we search that record, that Social Security number, both on our national DDR and our local donor records.

Again, it's used at our mobile sites as well as our fixed sites, and it applies to allogeneic and directed donors only.

When we implemented pre-check, it was never intended to replace, again, any of the other screening measures that we use in our donor belt line. It does not screen and was never intended to screen anything other than allogeneic and directed donors, and it was never intended to be our final screen of record. Our final screen of record continues to be our DDR check back at the blood center.

The goal that we had with pre-check was to reduce collections from ineligible donors, and again, it was to select those donors specifically who were attempting to donate before their appropriate deferral time 56 days, those donors who were indefinitely deferred previously, as well as donors who have a temporary deferral with a known eligibility date.

The way the process works -- this is the high tech. part -- is that from our host system we download information at the center from our host

system, both the national DDR and then our local donor records, and this is where the 56 day interval information would be. We download that to a PC.

Here all of the extraneous information is streamlined. We only then take down information, including the Social Security number and the eligibility status of the donor to the hand held device.

The equipment associated with this aside from the PC that you just saw and the information coming down from the host computer systems is, again, the hand held computer itself. It's run by a nicad battery. Also in here is a lithium battery. There is an AC adapter so that you can plug it into a wall.

We needed universal battery chargers to keep the nicads going, as well as the cables that are used to actually do the download from the PC to this unit. So that's kind of in a nutshell what comes with this package.

Our regions have several of these hand held computers, and so to do the download procedure, the cables that we use allow downloading the information to about 15 computers, 15 hand held computers at a time. You can do 15 hand helds in about 15 minutes. So that streamlines our operations a little bit.

On average our larger regions have about 50 to 90 of these hand held units, and the smaller regions somewhere around 20 to 30. So we needed to be able to download to more than just one unit at a time for those reasons.

The way pre-check works at the collection site is before a donor completes the registration process, before they go through the health history question, and obviously before they have a needle put into their arm, we go through the pre-check process.

And the way that works is that the collection staff requests from the donor some piece of identification that has their Social Security number on it. If the donor does not have a driver's license or something with their Social Security number, we will just ask the donor for their Social Security number.

The collection staff then entered the Social Security number right into the pad here, and there are several options that will come up on the screen. If the donor is eligible today, then the message today will appear right on the screen.

If there is a potential match of that donor's Social Security number on our donor or deferral list, then there are two other scenarios that could happen. If the donor is indefinitely deferred for some

reason in the past, the message "may not donate" will appear right on the screen.

If the donor has either not completed their 56 day interval or they have been temporarily deferred but have a next eligibility date, then that date that they're next eligible will also appear on the screen.

If a donor -- for either of those latter two reasons the donor is not eligible to donate on that day, they're given a letter with a phone number where they can call for additional information. That's an important note because this is very confidential information, and what we really didn't want to have is the staff at the collection site having to be in a situation where they were having to explain to a donor in some cases very sensitive information.

So the collection staff have no idea why the donor is not eligible to donate that day. All they know is that they are ineligible to donate that day, and they have a place where they can go to get the information.

So when we started down the path of implementing a system like this, there were obviously a lot of policy decisions that we had to make at first, the who would be checked with this, the what, the where, and the why. So we went through a quite

extensive task force of looking into those policy decisions.

Then we went down the path of developing the different software systems that were required for this. At that time, of course, there was nothing off the shelf that we could purchase. So we had to develop it ourselves. So there is very specific software that is in the hand held that we developed. There is software that needed to be developed to actually do the download from the host, and then from the PC to the hand held.

And then we went through a hardware selection process. So this hardware has been around for a while. We had a lot of requirements for the hardware. Specifically it had to be rugged, and it had to be able to pass a five foot drop and still work after repeated five foot drops, and as you all know, things do get dropped in the blood mobiles, and we're still trying this out on a daily basis.

So we've had to develop the procedures and training to implement this. The IS staff were a group that had to be trained on the download process, and that was the IS staff at every region location, and the collection staff needed to be trained on the function use of this out at the blood mobiles.

The interesting thing about the training of the collection staff is that we implemented this back in 1994, and what we found is that most of the collection staff had never really had any interaction with the computer, much less a hand held computer before, and so there was a lot of trepidation on their side for beginning to use a computer.

So we had to get through that and then the rest of the training. It's a fairly simple procedure to do.

We had to develop our response lines. Every region had to have an 800 number where the donors who were deferred at the collection sites based on pre-check or found out about their deferral, I should say, at the collection site could call in and find somebody on the other end of the line to understand why they were not eligible.

And then just the logistics surrounding hand held computers. So there are several logistic issues that we faced as we went through this, and what I have here is sort of like a laundry list, and I'll go through some of them in more detail than others, and then afterwards if you have questions about any of the specifics, I'll be happy to go into it.

But the power source for these was an issue

for us initially because we started with it allows the use of just a little alkaline battery, and that only was lasting for nine hours, and so we were having the power die off like into the second day of a blood mobile.

So we had to then switch to nicad batteries. When we switched to nicad batteries, it was much better, and the power lasted for about 40 hours, and so we were then into a routine where we didn't have to recharge for a week.

The issue then became recharging the nicad batteries themselves and setting up a process to do that.

Download frequency. Our policy is that these records need to be refreshed every seven days, and so that was a process, again, that had to be put in place to make sure that that refresh happened and that the computers would not be used unless they had had that refresh.

The equipment problems that we experienced up front were mostly hardware related. Even though they're very rugged and can withstand five foot drops, sometimes we drop them for more than five feet off of trucks and so forth, and so we had several experiences with broken springs and loose cables and so forth, but

we really -- as the regions got more comfortable with them, they began to treat them better, and we have had relatively few problems with that going forward.

Again, all of the scheduling associated with this, when you have a large region, for example, that's got 90 of these, you have to schedule refreshing in seven days and making sure that there are units out on the other blood mobiles still able to be used, charging the batteries, and so forth. It sounds like a lot, and I guess, you know, initially to set it up, it is, but once you have a process in place with a schedule, it just becomes fairly routine.

We needed to deal with security. It looks, you know, like a fun unit, you know, like there should be games on here or something. In fact, there really aren't any games on here. People wanted to know if they could install games, and we discouraged that.

And so we still initially had some issues with losing these small units, and so we had to develop some security measures around that.

And then just the cleaning, we -- because they were being used at the collection site, most often at the health history table, there was the potential for small drops of blood to get onto the computer, and so we had to develop procedures, specialized procedures

for cleaning the computers.

We found we couldn't store the computers on our trucks overnight in the winter. They didn't work in the morning because thy didn't like those freezing temperatures.

And then just all of the -- associated with the scheduling and the processing and where to keep these units, we had to develop processes and specialized resources for managing this.

So was it all worth it? We decided that we absolutely needed to measure before and after data with our experience with pre-check.

With Region A we had a total of ten months' worth of data, a total of almost 200,000 presenting donors, and of those 200,000 presenting donors, we had 959 -- this is data that's back from 1994, exactly when we implemented -- 959 that were a pre-check hit. That means they were not eligible that day when they showed up to donate. That represented .48 percent of those records, those donors that were, in fact, not eligible.

Region B, slightly fewer months, slightly fewer total donors that we attract, but still 522 deferrals caught by pre-check which represented that percentage. And so a total for those two regions alone was .38 percent effectiveness.

Okay. We decided we needed to really understand who the donors were who we were capturing with pre-check, and so of that Region A, a total of 959 donors, 452 of those donors who were attempting to donate were attempting to donate too soon. They weren't deferred. They just weren't eligible yet. This is Region A, and 507 of those donors were actually DDR hits. So they could have been temporary deferrals; they could have been indefinite deferrals. We didn't break it down to that next level, but they were DDR hits.

Region B, you'll find something similar. Again, we had 231 of the 522 donors were attempting to donate before their 56 days were up, and 291 were DDR hits. So this is how many donors just in two regions we captured with pre-check during a relatively short period of time.

And then just in Region A we did before and after measurements. So before they implemented pre-check they actually collected in a three month period 171 units that once they went through the collection process, got the unit back to the center and did our true DDR or tests of record DDR check, found that they were ineligible, which means that they had to be discarded.

At three months after pre-check, they had 20, and this is how many donors were the three months before and three months after. So it was a fairly significant reduction in our DDR hits that we were capturing in advance now of actual collection.

So the benefits that we've experienced and continue to experience with a system like pre-check is a reduction in collections from donors who are ineligible. It reduced our error rate associated with collections that we didn't need to be making anyway. It reduced potential staff exposure to these units. It reduced testing cost of units that weren't going to get used anyway, and it increased our collections from donors who were temporarily deferred because we were able to reschedule them right there at the collection site.

And it was truly our first process that was standardized with the computer through our system. So it sort of set a baseline for us to move forward with other systems that way.

Where we're going with pre-check in the future, as Richard had mentioned, you know, the technology certainly has changed in the last few years. So we're looking to actually be able to do things more real time and on line, and are looking at Web based

applications to do that. So we actually plan on doing on line screening at the collection site some time in the future.

And we, of course, want to be able to do this with all donation types, not just limited to allogeneic and directed.

In conclusion, we implemented pre-check in 1994. It was accepted readily by donors and by staff. There had been some thought that donors would be uncomfortable with giving us their Social Security number and seeing us enter it into a computer. In fact, the donors thought it was a great new thing, and we really received very little negative feedback from our donors on this process.

It's easy to use, and it's confidential. There is nothing on these computers other than the Social Security number and an eligibility status, nothing about why the donor may not be eligible to donate.

So .38 percent of presenting donors are deferred with this device, and 54 percent of these deferrals represent DDR hits, which resulted for us in an 87.5 reduction in post collection DDR hits, DDR and donor, I should say, hits.

So I guess we're taking questions on the

podium later. Thank you very much.

DR. FENNER: Thank you, Stephanie.

Our next speaker is Dr. Dale Malloy, who is the authorized official for the Florida-Georgia Blood Alliance in Jacksonville, Florida. He's representing the American Association of Blood Banks, and he's going to speak on the implementation of the donor deferral registry.

DR. MALLOY: Our facilities in Jacksonville, Florida are licensed by the Food and Drug Administration and accredited by the American Association of Blood Banks.

Next slide.

You saw earlier references to the Code of Federal Regulations' requirements for records of donor information. So we'll move right along to the next slide, and tell you that the AABB also has requirements in its Standards, and like the FDA, the philosophy is that a unit of blood's quality should be reliable regardless of where it's collected, whether it's on the mobile or at a fixed site.

The 19th edition of AABB Standards paraphrase says that records shall be retained indefinitely. They should be retrievable in a period of time appropriate to the circumstances including,

among other things -- next slide -- records of prospective donors who have been indefinitely deferred or placed on surveillance for the protection of the potential recipient and donors temporarily deferred for recipient protection shall be maintained for the deferral period, including interpretations of pre-screening and qualifying tests, and there are also requirements for error and accident recognition and management.

Next slide.

The AABB has a wonderful publication called the technical manual, and this manual tells you some of the "how to's" for dealing with these. One of the things you want to be sure you do is is identify the donor and link the donor to existing donor records. Otherwise you don't have much help here.

The records should include the reasons for prior deferrals, and like the previous speaker, our system does not include the reasons at the mobile site or even at the fixed site at the registration area. The person handling that does not have the detail level.

Persons indefinitely deferred should be identified as such prior to making blood available for release. We heard that in the FDA requirements as a

safety issue, but ideally you should have this information available prior to the collection.

The goal is that systems much prevent the release of blood from such persons if the info. is not available prior to the collection.

Next slide. And the next one. I'm sorry. I'm out of order here. Goodness. There we are. Thank you. That's where I want to be.

So we do have a range of options currently available to us. You actually can go out on a mobile or even at a fixed site and collect blood simply screening the donor according to standard procedures. You can take the blood and enter it into your computer system if you have one, or you can simply go back to manual records and look up the donors if you use a manual system there.

You've heard that you can periodically download portions of the database to hard disk or using compact disk or other technology, and you actually can today in many cases use real time wireless access.

Next slide, please.

Now, I was asked by the AABB to develop this presentation. From here on I'm on my own. So you should consider my comments to be mine this morning.

Florida-George Blood Alliance serves a

seven county area centered by Jacksonville, Florida. It's primarily urban. Approximately 60 percent of our collections are on mobile units, and we collect blood within approximately a 50 mile radius of the greater Jacksonville, Florida city there.

Next slide.

When we began analyzing our donor registry, on mobiles particularly, we were using handwritten donor records. We would monthly print out deferral records. We had two lists, a permanently deferred donor list without the reason, and a temporarily deferred donor list.

When the mobile would fully collect the blood and go back to the main center, the records were then entered into the computer, at which time we would find that we had collected blood that did not meet qualifications there.

The data you see here in this slide showed the total number of registrations by year for the years 1996 through 1999, and it's important to note that our SOP requires that we not draw blood from deferred donors. So you know I'm going to tell you that we had some variances from our SOP.

Next please.

And what we found is that in the year 1996

we had 127 out of some 60,000 donor registration incidents where people either donated too soon or they had other temporary deferrals, and they had permanent deferrals, and I'll try to get this pointer working here.

The permanent deferrals are the blues, and this is, again, over the period of time from 1996 through 1999. The early donations are shown by the orange, and the other temporaries are by the whites. We'll talk a little more about that.

Next slide.

Now, in 1996, we had establishment inspection report comments, and this was before the -- actually we were just moving into the FDA's kinder, gentler mode of activity there, and we appreciate that, by the way, that they have done so.

In 1996, we were noted informally obviously that we had a failure to establish and implement methods to prevent ineligible donors from being drawn on mobiles or during portable drives, and being the responsible authority according to the FDA, I had a strong interest in doing something about that.

In 1997, the entry has changed. You can see the FDA believes we've done something to change that, but we're on the way but not there yet. And they

said we're going through extensive evaluation of using laptops on mobiles in a real time mode. The donor would be registered on line, and a donor card would be printed at the mobile location.

What we've found at this time, that that particular technology in 1997 was cumbersome and slow. It took a long time to registered a donor, and it was going to cost us about $300,000 a year as a small organization compared to the National Red Cross, and that was going to be cost prohibitive.

Along about there we had some changes in technology that make things vastly different.

Next slide, please.

Now, the concerns that these comments reflect are that no blood from an unacceptable donor be distributed. We're unaware that we had a problem with that. We believe we did not have a problem with that, reminding you that it is permissible to reliably accept blood at any stage, preferably even at recruitment, but at registration or any time prior to labeling.

Another concern was donor safety and service. Drawing people too learn creates iron deficient donors, and you don't get to use that unit of blood unless you document it as varying from your SOP. So there is a fair amount of cost in terms of lost

effort and even lost donors by drawing them too early.

The other thing we found, I think all blood centers probably get return mail in which donors have been attempted to be notified, but in fact don't receive the notification, and by not having access to the information ahead of time that a donor is disqualified we don't have the ability to say, "You're not supposed to be here. According to this record, we sent you a letter on such-and-such a date. Please call this number."

Additional concerns revolve around control. Our SOP prohibits collecting disqualified donors. We were operating out of control some of the time, and on busy mobiles we did have, as I said, written permanent deferral records, lists, and written lists of temporarily deferred people, and in the press of business, people did not see those names from time to time on those records there, even well trained people.

And when the data are a month old, you have to question how valuable that is, how complete it is, and we now do have on line donor checking, and it is, of course, current.

And one other thing we found is we were looking at donor retention and trying to do some donor recognitions, and I hope nobody is making notes on

this. We actually found a small number of donors who donated as many as eight times a year.

We also would occasionally, and we still do due to limitations in people's presentation of information, have occasional duplicate donor records, but one of the things we wanted to do was to reduce reportable errors.

Next slide, please.

And as you've heard -- next slide. I think I must have gotten ahead of us here. Thank you -- you don't want to collect a unit that you know that you don't want to be exposed to. You don't want it in the house at all, and since the quarantine systems are not foolproof, if you don't draw them, you don't have the risk of then getting out.

Next slide.

What we were able to do is develop a system using laptops and wireless modems in which we actually access our mainframe computer live. The data are transmitted via modem. There are dedicated radio frequency channels, and the data are broken up into packets on one end and reassembled at the other end. They go through an intermediate system, through a router, and through an AT&T network.

And I don't mean to do a commercial for

AT&T. That's who our vendor is, and we could not do this without them.

Next slide.

What you see here at the bottom of the page is the vendor map. That's a little out of focus. I think I can talk through that if I need to here. Thank you.

In the bottom is a system map which shows the signal strength, and we haven't conducted any mobiles that I know of out in the Atlantic Ocean, but just in from there, all up and down the coast you'll see that we have very good wireless signals and can operate our mobiles effectively.

We draw a fair amount of blood on a military base. We had poor signals there. The military base is located right up in this area. What you can see has no signal reflected there, and we wondered if the military wasn't using security measures to prevent wireless transmission.

That turned out not to be the case. It turned out that there are simply an inadequate number of cell phone towers there.

Another thing that we found is that this center right here is located right in the edge of this area, and it happens to be across state lines, and if

you've ever tried to work with telephone companies setting up things across state lines, everybody's responsible, which means nobody's responsible. It's extremely expensive to have a technically decided long distance phone line open 24 hours a day, and what we did was put a wireless unit in that particular location and saved about $1,000 a month in long distance calls.

We have laptops on each of our mobiles and also on our portables there. They go through the AT&T wireless CDPD network and then into a frame relay system that we have, and we have each of our centers set up on the frame relay system. We have the Internet connection on the frame relay system, and then we have as one node on the frame relay system our own computer network, which includes a set of PCs on the network and our mainframe computer.

Next slide.

And you think about security. We're putting these data out over the air, and you say, "Well, gosh, how wise is that?" We have multiple levels of security that are included here.

The first level is that the signal is digitized. It's also encrypted by the AT&T people. The data packets are split up into packets and require reassembly at each end.

You also have to have the application software in order to capture and use the data. There's a firewall. You have to have a password to get into the system, and then we have our own private frame relay.

So we believe that we have pretty good system security here.

Next slide.

You say, "Well, how do you do this?" I believe if it weren't for the Jacksonville Electric Authority, which is a big user of this technology, and the Duval County Sheriff's Office, which also is a big user of this technology, we probably would not have the kind of support that we have.

As it is, the vendor has been very responsive. Twenty-four hours a day we're able to get help, and we do do some collections on the 11:00 p.m. to 7:00 a.m. shift at some places there. So that is important.

Next slide, please.

We have personal computers and wireless modems that are permanently installed on our two newest mobiles. We have others that are installed temporarily on the mobiles, and the permanently installed ones therefore don't have to be rewired and recalibrated

every time they're set up, and they don't break.

The ones that have to be transported into and out of the mobiles don't withstand the five foot drop test that we heard described earlier, and we've had a few replacements there.

I've already mentioned the substantial savings in long distance phone calls by using this technology in one of our centers, and I'll tell you that over 90 percent of our mobile registrations are done on line, and the speed, because of the technology, is transparent. It's essentially the same at a fixed site and at a mobile site.

The staff are well trained, and as we heard described earlier, our staff have seen computers. Even I could do this. I can spell "computer" correctly most times unless I'm trying to type it. You don't have to be especially knowledgeable about computer technology to be able to do this.

Especially if we leave the computers hooked up on the mobile units, they are almost foolproof. We get about one call a week to our technical person, and sometimes those are not computer related problems so much as they are operator related problems.

Now, early on our staff resisted using these things. We were asking them to change from a

familiar write your information down on a sheet of paper process to one in which they were expected to keyboard information accurately with the emphasis on accuracy.

And, by the way, they were willing and did for many, many years return to the blood center after conducting a blood mobile donor collections and may have to register two or 300 blood collection records at ten o'clock at night. Obviously now they don't want to be without this support.

We also have begun to use bar coded donor cards not only to ease the donor registration, but to also improve the accuracy.

We've seen a change in error rates that we've experienced. We've normalized the error rate here per 10,000 registrations, and you see in 1996 we had just over 20 errors per 10,000. That was when the FDA first said, "Hey, we have a problem here that we're concerned about."

In 1997, when the FDA observed we were working on it as hard as we could, we actually had an increase in the error rate. We were struggling there, but we were working on it hard, and in 1998 we began to see the payoff here. We saw a decrease in the error rate.

And when I say "error rate," I'm talking about donors being accepted who were either temporarily deferred, permanently deferred, or who were less than 56 days out from their last donation. In 1998, that number then was down about a third, you can see, and in 1999, it dropped down to 3.3 occurrences per 10,000 registrations, and I'm happy to tell you that there were no permanently deferred donors in that group in 1999.

Those occurrences happened primarily when we did not have adequate wireless access.

Next slide.

There are some issues. The equipment is expensive. Wireless service is not available in every location where we set up. Sometimes the signal strength is inadequate. Occasionally you get interference with signals, and technical support is important not only in your blood center operation, but also with your wireless phone vendor there.

Customer service, if your wireless is working well, you look very positive. You're able to tell donors information from their past donations that is useful and interesting to them.

On the other hand, if the wireless is not working well, you experience delays and you come off as

a boob, and so there are remaining issues in customer service, and it is imperfect, but getting better almost daily.

Next slide.

Now, when I came I had a limited understanding of what kind of national databases might be expected by the FDA. So I added just a thought or two.

I think we do have inconsistency within a single institution and from institution to institution regarding donor identification, and so I do have some concerns about a national deferred donor database, even those that are currently in use.

I believe that donor deferral criteria differ among institutions. I did see a nice model presented this morning in terms of limiting the kind of information that would go into such a national registry if it were ever considered.

I believe there are systems compatibility issues. Those can be overcome, but I believe they're real at this point.

And we've heard concern about how much information to make available in the face of variable confidentiality laws around the country, and of course, we've also heard that data's timeliness varies from

immediate to a week to a month to maybe never.

Next slide.

I want to talk just a little bit about costs, and I apologize because this slide is a little bit mixed up. For $4,000, you can put a PC, a bar code scanner, a printer, and a wireless modem on a mobile unit. It takes about a day of training to have someone who is on-the-job trained learn how to do this pretty reliably.

There is a requirement for troubleshooting and vendor technical support. You also have to have frame relay lines, modem registrations, and modem set-up fees, but from there then the charges are flat rates by our vendor, which makes the procedures we use very affordable.

Our combined annual usable cost, not including -- I'm sorry. Let me back up and try to say this right.

Annually we spend about $15,000 to provide this service to ourselves, not including the equipment cost. You amortize the equipment over a period of time there.

Now, $15,000 on a budget of about ten million is certainly not a very large cost.

Next slide.

And in conclusion, the benefits we've seen are similar to the others you've heard today. Early collections are reduced. We see less wastage of staff effort. We actually have legible donor records. What a blessing to look back in three years and be able to read these things.

We have reduced staff exposure to biohazardous material. We appear professional and state of the art, and our systems are now more under control and getting better by the day.

Thank you.

DR. FENNER: Okay. Thank you, Dr. Malloy.

We're really running quickly here this morning. So our last speaker on this topic is Dr. Merlyn Sayers, who's the authorized official for Carter Blood Care in Bedford, Texas, and Dr. Sayers is representing America's blood centers, and he's going to talk about the implementation of the DDR.

DR. SAYERS: Thanks.

I do appreciate this opportunity to speak to you on this topic. I'll have to say by way of a preface though that if any of you suspect that you've heard some of these remarks before, let me assure you that your suspicions are well founded. The only difference is that some of these remarks I do have a

chance now to deliver before an FDA audience.

Something about the goals and objectives that intrigued me when I read the announcement about this workshop had to do with the sentence which included one of our responsibilities was going to be to evaluate how donor deferrals impact the national blood supply. So I am going to make some additional comments on that topic.

My affiliations, certainly America's blood centers, but let me say that I am not offering a position statement for America's blood centers. Certainly I am a trustee, but my remarks reflect some concern of myself and other members of ABCs having to do with donor deferral registries, but I must emphasize that this is not an ABC position statement.

Carter Blood Care in Bedford, Texas is politically equidistant between Dallas and Fort Worth, and we are a community independent blood program.

Let me harken back to something that Larry Fenner has said in the prologue to this workshop. He said that he did not expect us to share information with our competitors, and I wondered for a while what he was getting at about that, and then it occurred to me that there is another organization which is enthusiastically drawing blood donors at the perimeter

of our service area.

We do not see that organization so much as competitors at least in Texas as allies who have a similar mission, and the only difference is that their head office is in Washington, D.C., whereas ours is deep in the heart of Texas.

(Laughter.)

DR. SAYERS: Let me say something about the function of donor deferral registries. Can I have the next illustration, please?

I think we need to remind ourselves that in considering DDRs one of the essential goals is to retain information that is pertinent to the safety of the donor. I mean we would not nationally be able to draw or continue to draw or continue to try and draw 40,000 individuals a day if it were in any way an unsafe intervention, and certainly one of the ways that we insure safety is by having deferral registers which insure that we do not draw donors under circumstances which would be injurious to their health.

And then secondly, it's obviously important that we retain donor information that is relevant to the safety of future transfusion recipients. Have those donors expressed risk behaviors in the past? Do they have serological markers for infectious disease?

Have they remembered to tell us about travel to dangerous parts of the country riddled with plasmodium and goodness knows what else?

Essential information that is relevant to the safety of the transfusion recipient, and then more recently -- next, Joseph -- another reason why donor deferral registries are becoming important has to do with we need to retain that information that's going to permit us to lick the temporary deferral, such as the history of transfusion or the history of the recent tatoo.

The extent to which we are driven to conserve every single possible donor that we can places additional emphasis on the value of the donor deferral registry when it gives us an opportunity to identify those donors in whom temporary deferrals can reasonably be listed.

There are shortcomings when we consider the donor deferral registry, and the FDA has understandably and very legitimately emphasized on a number of occasions that there are layers, numerous layers of transfusion recipient protection, such as voluntary self-deferral, the medical history, the examination of the donor or be it a very abbreviated examination, confidential unit exclusion, the opportunity that a

donor gets to answer all the questions in a less than forthright fashion, but enable us to withdraw his or her unit from inventory by confidentially excluding that for the purposes of transfusion, and then obviously the serological testing, both the conventional testing and more recently the NAT testing.

Another layer of protection is the telephone call-back. We encourage donors to phone us if they have second thoughts about something or if a partner or a spouse reminds them that they had, indeed, spent six months and one day in the Channel Islands between 1980 and 1996.

And then there's hearsay information, difficult to handle, but certainly we have to take into account as one of the layers of protection the fact that some individuals might bring to our attention through good reason or through perverse reason, might bring to our attention the fact that some donors ostensibly suitable are privately and for reasons that they fail to reveal to us, privately inappropriate donors.

And then we get transfusion transmitted infection reports from hospitals and physicians, information at every single level which would enable us to update a donor deferral registry.

Nonetheless, the donor deferral registry's actual contribution to safety, what it does in terms of reducing the risk of transfusion transmitted infection is not known.

It's interesting when we review what our experience has been with donor deferral registries over the last ten years. One would have thought that with increasing sophistication on the test front, there might be less reliance on the donor questionnaire. Surely as we identify tests which will pinpoint individuals who are, for example, likely to transmit non-A, non-B, non-C, whatever hepatitis, then there would be less insistence on questions like have you ever had jaundice; have you ever been exposed to hepatitis.

Exactly the opposite has happened. Look at these figures here. In 1988, we asked donors 22 questions, and the number of responses that was required of those 22 questions by virtue of the fact that questions contained within them additional questions was 46, and then in 1999, we are now asking donors 50 questions, and the number of responses is 82, and that is even after we have eliminated from that questions section 25 questions that are read by the donor having to do with risk behaviors.

What is the national experience with deferral of donors as a result of some of these more recent considerations?

These are individuals who have registered at America's blood centers in 1998, and this was a survey which was conducted by Celso Bianco from the New York Blood Center. He looked at something like four million donors who had registered. Of those four million, something like half a million donors were deferred, and they were deferred in something like 34 different categories of deferral. Each one of those categories of deferral earning an entry in what is becoming an increasingly cumbersome and complex donor deferral registry.

So 13.26 percent of donors on average were deferred, and this was a deferral which was not related to any serological test results. These were deferrals up front, prior to deferrals for testing.

The range at these blood centers which were in excess of 40 blood centers taking part in the survey was a low of 3.43 percent of deferred donors to a high of 34.46 percent of donors presenting at registration only subsequently to be deferred.

If you translate that figure to what might be national experience, something like 1.8 million

individuals who ostensibly feel healthy and present themselves as candidates for blood donation are deferred. One, point, eight million are deferred a year prior even to any testing has been performed on them.

What this illustration shows then relates back to the study that Celso Bianco did, and it looks at the averages and the ranges for some of the deferral categories. I haven't listed all 34, but for some of the deferral categories, looking at what the low deferral values were and what the high deferral values were.

Now, the commonest reason for somebody at one of these 42 participating blood centers to be deferred, the commonest reason obviously was a low hemoglobin. The average was 5.39 at a blood center which had presumably perhaps a high male donor population group. The hemoglobin deferral was only 1.42 percent.

Alternatively, maybe it was a blood center which relied significantly on first time donors, not on repeat donors. The high hemoglobin deferral rate was 20.3.

Blood pressure was another common reason for somebody being put on a donor deferral registry.

An average of 1.1 percent, a low of .14, a high of 4.97, implying that those individuals, 4.9 percent of the individuals presenting for history and examination had a systolic blood pressure which was greater than 180 or diastolic pressure which was greater than 100.

Tatoo. There is this sad epidemic of ritual mutilation which is sweeping the country, and I had really thought that this was something which was perpetrated only in the grunge parts of Seattle, but I mean, certainly it does appear to be a national phenomenon.

The average for deferrals is nearly .7 percent, and it's high at 1.51 percent possibly at a blood program which relies particularly on school age donors registering to contribute to the local inventory.

High risk groups, we might assume that the blood center which had no individuals added to their DDR as a result of a high risk group might have been from somewhere in the heartland, whereas the blood program that was adding one percent in this category was probably from a metropolitan area.

What we did with some sort of perverse curiosity was add up for those more than 40 blood programs what the lowest likelihood for addition to a

donor deferral rate might be, and that was by adding up all of those low values in the 34 categories.

So at the very, very best, if anyone's blood program reflected the minimal experience, then 1.97 percent of donors would be deferred and added to a donor deferral registry. If you added up all of the worst case scenarios, then you could achieve nearly 61 percent of the donors being added to the donor deferral registry because of their responses either in the history or in the examination.

What does all of this meandering mean then in terms of establishing and implementing donor deferral registries? I mentioned earlier that Carter Blood Care is the merged program. When Dallas and Fort Worth, now Carter Blood Care, considered merging their two programs, there were those that likened this preposterous possibility to bringing together the Montagues and the Capulets or the Hatfields and the McCoys.

But nonetheless, Dallas and Fort Worth now do have a merged community independent program, and one of the challenges during the discussions bringing these two programs together had to do with how clean is the donor base, the donor deferral registry in particularly in Dallas, and how clean is the donor deferral registry

in Fort Worth, clean not in the sense of the unrighteousness of the donors, but clean in terms of are there duplicate entries. How corrupt is the information? How accurate is it?

So what we needed to do was look through each individual blood program's donor deferral registry to find out whether there were, in fact, duplicate entries which needed to be scrubbed before those two separate but now clean donor deferral registries were actually merged into one.

So we developed computer programs. We looked at these 550,000 individuals in each on either side of the county line and looked for possible duplicates, and in fact, what we found were 596 possible duplicate pairs.

What did a duplicate pair consist of? Well, there were a myriad of examples, but an individual might be considered a duplicate because he or she had a same Social Security number as one individual, but a different last name, or in one of the pairs the Social Security number might be absent, but the pair shared the same name.

We also looked at the possibility of individuals who might be duplicates because there was a single figure difference in the Social Security number

or if there was a transposition of figures in the Social Security number.

And then there were other variables. There were birth dates. Gender was a variable. Did people have all the same information except their genders were different? Was Pat on one donation a male and on another donation a female?

So 272 of these possible pairs that our programs revealed were false duplicates. They actually were different individuals. So they had different donor deferral characteristics legitimately.

Three hundred and twenty-six though were true duplicates. These were the same individuals. So we were able to merge what looked like discrepant information, and we were able to come up with individuals who -- could I have the next slide? -- come up with a donor deferral registry for each of those two blood programs which did not include individuals whose information was duplicated.

What was the yield here? When we merged these true duplicates, we found that three donors who were not previously regarded as ineligible actually now deserved permanent deferral. All three of the donors were duplicated because of mismatched Social Security numbers. Two had repeatedly reactive HTLV-III results,

and this gives you an idea of how old this information was.

(Laughter.)

DR. SAYERS: These were individuals whose duplicate entries occurred in 1986, and in one record only, and the other had a repeatedly reactive anti-HCV result in only one record.

So we cleaned up our donor bases, merged the two, and then discovered that we had three individuals who should have been ineligible.

We also had 1,800 individuals when these donor deferral registries were merged, 1,800 individuals who through no fault of their own, but through the fault, for want of another term, of merging these two registries suddenly became deferred. These were the individuals how had a core antibody during a donation in Fort Worth on one occasion and a core antibody during a donation in Dallas on another occasion; individuals who had an HTLV on one occasion at one center and an HTLV on another occasion at a different one.

Then with merger of those two donor deferral bases, we ended up with 1,800 individuals who, ye verily, it came to pass were angry.

(Laughter.)

DR. SAYERS: The public relations challenge that the merger of these two blood center deferral registries posed, the public relations challenge was significant, but we certainly do believe that it was a very necessary element in the successful merger of two contiguous programs.

Let me say a few words about implementation obstacles, and we've hinted at some of these. The consistent, the accurate, the unique identification of the donor is a challenge. It really is a challenge.

There's the old fashioned habit in Texas that when women get married they change their name on some occasions to that of their husbands.

(Laughter.)

DR. SAYERS: And this may be a folly which is not perpetuated through the rest of the country, but certainly it does impair our ability to be consistent and accurate and unique in identifying donors to insure that they are appropriately added to a donor deferral registry or a donor database.

Multiple records on the same donor. A donor deferral registry is only as good as those multiple records are eliminated. One donor, one entry on the donor database and on the donor deferral registry.

Managing changes in deferral status is something that is also a challenge. The deferral status can be permanent. It can be temporary. Individuals can be reenterable with additional testing. These challenges have to be confronted for an appropriate DDR to be established.

And then step-wise deferral is also a challenge. Core antibody and HTLV screening are examples. A donor deferral registry has to be able to follow individuals who earn a flag at one donation, which is only raised to full mast on the acquisition of another serological test result.

Some of these obstacles that I've hinted at locally are obstacles which have also been encountered state-wide, and I know Dr. Holland has had experience with donor deferral registries in California, and I'm sure he'll be able to give us some information on what the challenges are at a state-wide level.

What about our experience then with the donor deferral registry as it is in these merged organizations? The donor deferral registry is actually taken to each mobile site in our merged blood program by laptop, and each registering donor is reviewed and access to him or her in the donor deferral registry is via the Social Security number.

Now, the DDR at our program is updated daily, and it's updated with whatever the current donor database is, and that includes then the most recent serological test results and any other information about donors that has come in from hospitals or from clinics or from physicians' offices.

So we looked at August, September and October of 1999. What was our experience with reviewing the DDR at the time of registration for 37,588 donors? This is what we found.

Nearly 15 percent of the donors were deferred at registration. They were deferred by computer in our parlance 266 times. Now, the majority of those 266 individuals who were deferred by review of the donor deferral registry at the time of registration, the majority were individuals presumably whose enthusiasm to donate had reached such outrageous proportions that they confused the calendar and had presented themselves too early. These were the stalwarts of the program who were coming in at day 52 or day 53, but the majority of those DDRs were individuals who arrived too early.

Is there a safety element there? I suspect there is a modest safety element. You do not want to draw somebody too soon. You might jeopardize their

iron balance, but for a blood program, a not for profit community blood program that is nibbling away and trying to get some tiny morsel of this shrinking health care dollar, there is an important economic consideration here, and that is not drawing somebody whose unit you would subsequently discard because they had presented prematurely.

And I do not want to make this a finances issue, but being able to defer individuals who present prematurely does make economic sense for the blood program.

A much smaller number of individuals were individuals who alerted us to how we should change our donor notification process because they had misunderstood a telephone call about not donating or they had misunderstood correspondence, but those individuals were in the minority of that 266.

Now, you might be interested in the major elements of those 5,626 deferrals for that three month period, and certainly hemoglobin deferrals accounted for the majority. Vital signs, temperature, pulse, blood pressure accounted for 1,051, and even in Texas there are people who are puncturing and perforating and otherwise rendering themselves grotesque all in the interest of cosmetics.

(Laughter.)

DR. SAYERS: I'd like to just return as I hinted at earlier to an element of the goals and objectives and comment on how donor deferrals impact the nation's blood supply.

And, Joseph, I'm going to need the projector for three slides, sir. So please bear with me while we get this going.

Statisticians are reasonably sharp individuals, and what we asked them to do was come up with an illustration of how we might link the relationship between the number of donations that a donor might make, the specificity of a screening procedure, and the likelihood that that individual is going to get deferred inappropriately. These illustrations have nothing whatsoever to do with appropriate deferral of donors as a result of, for example, screening test positivity and confirmatory test positivity.

Joseph, this is really a puny little shaft here.

(Laughter.)

DR. SAYERS: So what we're looking at then along this axis is the specificity of a screening procedure.

Here's a screening procedure of high specificity, 90 percent. Here is a screening test of low specificity, 50 percent. Here are the number of lifetime, weekly, or monthly donations that an individual might make between zero, increasing. Lifetime, 20 or so if it's a whole blood donor, or over a shorter period of time, for example, for a pheresis donor.

And this is the 90 percent chance that an individual is going to get deferred for reasons related only to specificity in the assay. So if we have assays of high specificity, an individual has a 90 percent chance of being deferred after 20 or more donations.

As that specificity declines, that individual has a greater likelihood of being deferred after much fewer donations, only four or so.

Let's have the next one, please.

We're inclined to think of specificity exclusively in terms of the serological testing, but I showed you earlier an illustration which showed how our questioning of the donors has become exuberant, and each one of those questions has inherently specificity and sensitivity. Frequently neither of those qualities measured in relation to any of the questions that we asked.

Let's go back one. There should be a third on there unless it's fallen out. Yeah, let's stick on that one.

So what happens then when one accumulates all of these specificity issues? Is it reasonable to predict that what we're going to achieve is specificity which declines dramatically? I think it is.

And what we achieve as specificity declines dramatically is, as was illustrated in that earlier slide, an actual condition where what we are doing is discouraging participation by the frequent donors because what we're doing is increasing the individual's likelihood that he or she is going to be deferred for reasons of nonspecificity.

I mean intuitively it makes sense. If you're going to be subjected to a question which has nonspecificity or a test which has nonspecificity, the more often you expose yourself to those circumstances, the greater the likelihood that you're going to fall afoul of that system.

Joseph, let's have that illustration now with those bar graphs.

When it first occurred to us -- the bar graphs -- when it first occurred to us back in '92 that we were losing regular donors, we wondered how we could

test what, as I said, seemed intuitively right, that the more often you donated, the greater the likelihood that you would be deferred, and came up with the thought that what we should do is look at discrepant results in autologous donors.

Now, bear in mind autologous donors are going to be accepted regardless of what their test results are and regardless of what their responses to questions are.

And because of that, we would be able to follow those individuals throughout their history of donation. So this is what we established.

In this column here are autologous donors who donated twice. These individuals donated three times. These, four, and these individuals five, six, or seven times.

And then we asked: how often do those individuals at those different donation frequencies have a discrepant result, an indicator of nonspecificity, an elevated ALT on one occasion, but not on another; core antibody on one occasion but not on another? And this is what we found.

If you donated twice, you had a one to two percent likelihood that you would have a discrepant result. When you started donating five, six, or seven

times as an autologous donor, your likelihood that you would have a discrepant result though had a fourfold increase of nearly eight percent, confirming what we had suspected and what seemed intuitively right, that individuals who are subjected to the perils of nonspecificity do manifest an increasing deferral rate.

Let me just finally then make some remarks about DDRs in general. We can have that slide off, Joseph.

Donor deferral registries at least as far as reducing the risk of transfusion transmitted disease is concerned, those registries are less important now that we have really sensitive tests, and the bulk of entries into DDRs, namely the history and examination entries, as opposed to serological results, they do have unknown sensitivity and specificity.

We have to bear in mind when we're considering DDRs that the information needs to be accurate because we have accumulating evidence that temporary deferral of donors is a major disincentive to those individuals.

When we bear in mind with all the increasing number of questions the increasing time that it takes to donate, if we are to maintain the royalty of those companies that allow us to draw individuals on

their premises, if we're going to maintain their loyalty, we need to cut down the donation time. We need to streamline the questionnaire.

We really need to focus the questions on donor safety, and we need to focus the questions, too, perhaps on those diseases for which the screening tests are not available.

And lastly, I really don't want anything that I've said to be construed as a plea for less vigilance. I really don't want that to be the message, but given what is an alarming shortfall in the national inventory, we really have to be cautious and we have to validate the strategies that we invoke to defer donors, and we have to be particularly cautious against the background that any incremental benefit in safety for transfusion recipients is going to be incredibly difficult to measure.

Thanks.

DR. FENNER: Okay. Since we're running early, we're going to have the panel discussion before we break. So if the speakers from this morning would join us here at the table, we can take questions.

MS. CALLAGHAN: If anybody has a question, maybe you could line up because this is the only microphone we have here. So please.

DR. SIMON: I think I have the obvious question to lead off, and that is our first discussant from ABRA talked about a national deferral registry with certain key information, namely serological data, were put in, and if the donor went anywhere in the country to a plasma donor center, it would result in a deferral.

All of the registries that we've heard about from the blood centers, both Red Cross and otherwise, result in a deferral if the donor returns to that particular organization. So the Red Cross has covered the Red Cross, and the independents have covered their various centers.

So I think the question is: should the blood centers of America, Red Cross and non-Red Cross, adopt a single deferral registry for the most critical information so that a donor who is excluded by Red Cross blood center, by let's say in Atlanta by the Red Cross, cannot cross the street and donate at Life South and be successful in being accepted even with a deferral that should have been permanent?

DR. SAYERS: Can I respond to that, Joseph?

PARTICIPANT: Larry is up there.

DR. SAYERS: Sorry. Larry. I'm sorry.

DR. FENNER: Well, certainly that's a good

idea. It's not within the scope of what FDA is proposing at this point only because we don't know the logistic -- we can't -- well, we just haven't worked out the logistics of doing something like that, and we don't know that it's in our purview, but if someone would like to do that, it would be great and they'd like to take it over.

MS. CALLAGHAN: Did you want to respond?

DR. SAYERS: I'm going to give a presentation later this afternoon, Toby, on cancer deferrals, and for eighty regulated organizations like blood programs, it continues to surprise me how much variability there is in behavior from one center to the next, and standardizing the donor deferral registry nationally I would regard as more than an uphill task, more of an impossibility.

And allied to that, I'm not convinced of how much that contributes to transfusion safety.

DR. SIMON: Well, I need to identify myself. Toby Simon from Serologicals and connected with ABRA.

But what I was suggesting is that the deferral registry be limited, as the one for the plasma industry is, to those things that are permanent deferrals as defined by the FDA, for example, positive

test for HIV, HCV, and so forth, in which there is standardization across the industry.

MS. NORRELL: There may be standardization in terms of who is deferred, but how you capture that information in your own individual electronic ability is vastly different, even until recently was different within the American Red Cross. Now we're on one system, so it's a little bit more standardized, but merging those records into one database would be a huge, uphill task, doable, but it would take a lot of work to get that done, to get the data to talk to each other.

We track these things by deferral categories, and I'm sure the other blood centers have their own categories for these individual kinds of test results and so forth. Those would all have to be mapped into common language.

MR. ROBINSON: I'd like to add in ABRA's experience the use of the NDDR for plasma donors is not in any way retroactive. So when centers came on line with the NDDR, they added the donor information in the format that was set up for the NDDR. We did not ask them to go back and add their existing databases.

So it was really sort of prospective, you know, from that point on. So once you had your

standard established, everybody followed the same rules, and we avoided, although we did not capture -- you know, there's a significant number of people who might not be captured if you did establish a national database, but prospectively as time goes forward you will capture an increasing number of those.

DR. HOLLAND: Paul Holland, Sacramento Blood Center.

I wanted to ask the panelists to comment on the use of their donor deferral registers in conjunction with state donor deferral registers, but before you answer, I'll give you one blood center's brief experience with the California state donor deferral register.

Our blood center draws about 150,000 units a year or about 450 units a day. Beginning in the 1970s in California, because of the risk of Hepatitis following transfusion, the state started a donor deferral register. It was required of all physicians in the state to report all patients diagnosed with viral hepatitis, all centers drawing blood or plasma to report donors with Hepatitis B surface antigen, and all centers that had donors implicated in cases of transfusion associated hepatitis either as single donors, in which case they had the generic category, or

as one of multiple donors, in which they had what was called the Category 9.

Subsequently to this list have been added HIV positive donors, HTLV positive I/II positive donors, and the HCV positive donors, and most recently HIV P24 antigen positive donors. Luckily we convinced the state not to add donors with an elevated ALT or antibody to Hepatitis B core.

The physicians and blood centers and plasma centers are supposed to report the name, address, Social Security number, birth date, sex, and county from which they're reported. The state updates this registry approximately twice a month, the 1st and 15th, by microfiche disk or reel-to-reel tapes.

However, there's a lot of incomplete and inaccurate information on there, and I'll show you the impact on that in just a moment.

This list constantly grows. There are now hundreds of thousands of names on it after 25 years. You cannot get off this list even if you were dead.

(Laughter.)

DR. HOLLAND: You can have your data come three different ways, as I mentioned, either by microfiche or by a disk or by reel-to-reel tape. We prefer reel-to-reel tape even though that has many

problems. The main reason we stopped using the disk is a lot of the state employees like to put computer games on there, and we didn't want that messing up our computer.

The biggest problem with this is really how it actually is used and what it accomplishes. With the number of donors we're drawing a day, at least two hours every day it takes technologists' time to sort through the matches by name and Social Security number and pick out those which are real or not real.

Some of them can be easily straightened out because of either sex or address or other things to show that they are non-matches, and that's true of the vast majority of them.

However, it takes another two hours of people's time the next day calling donors or physicians' intervention to find out which ones are real or not, that actually individuals had either positive tests or had hepatitis as a child or things of that nature.

So we're spending at least half of an FTE every day, and I would say we've gotten zero benefit out of this in terms of preventing, one, significant case of transfusion associated disease in a patient.

However, we do periodically audit the state

donor deferral registry, the first state which has about 34 million people. What we have found is that 15 to 50 percent of the data we report to the state comes out either inaccurately or doesn't come out at all. That is, up to 50 percent of the time people with positive tests for hepatitis, HIV, et cetera, never end up end up on this list despite turning the data into the state.

And even when it does get on there, many times it has the wrong Social Security number, wrong birth date or some other incorrect information.

In addition, about eight percent of them are true matches for positive tests, and as you've already heard, many people don't get the message even though they are told and we have evidence, and I'll give you one quick anecdote.

We recently tried to enroll an HIV positive donor in our CDC study that's follow-up with HIV positive donors. When we initially reported to the CDC, they said the donor is already enrolled in the study.

So we called the donor, and he said, yes, he had donated in San Francisco, been told he had a positive HIV positive test, was enrolled in the CDC study for risk factors and everything, but he didn't

believe it.

So two months later when he was eligible to donate, he drove to Sacramento, 100 miles away, and donated again, and luckily we picked him up with a positive test. That man, even though it had been two months, still was not on the donor deferral register, and even if we had been able to check it up front, would not have been stopped.

So my bottom line message is state donor deferral registers at least in California, I believe, are a waste of time. They cost us a lot of time, effort, and money and do not accomplish any good because of inaccuracies and really with the excellent tests we have, I believe we accomplish more by that.

So my question for the panelists is, again: how do you work with these state donor deferral registers on top of your own donor deferral registers because clearly you have to use both, say, in the State of California or other states that have this?

MS. NORRELL: I'll respond first. We've had actually a lot of problems with state deferral registries. As a matter of fact, just to carry on your story about the error rate with the information that's in those registries is affecting not only those individuals who are supposed to be on the deferral

list, but people because the data is wrong were actually getting confused with other individuals in other parts of the country who may happen to have the real Social Security number, where what was recorded in that state registry was either just recorded incorrectly or falsely or whatever.

And so then we're stuck with records and trying to figure out who really belongs to that Social Security number, et cetera. So that's been a huge problem for us.

We do, in fact, continue to use the California state registry because it's a state law. So we're required to, but I'm wondering if you're aware that that particular state registry is not yet Y2K compliant. So I'm wondering what you're going to do about that.

DR. HOLLAND: Actually that may be a very good thing.

(Laughter.)

MS. NORRELL: I thought it might be a real opportunity to address that problem, but we do also -- New Jersey has a similar state law, and we have some of the same issues with bad data from them, but it's not quite as severe as the California state health registry.

But I would agree with you that it's different requirements, different information that goes into those state health department records, and there's no control over those systems that we've been able to detect yet.

DR. HOLLAND: Yeah, I'd just like to add to that we actually -- I haven't counted the time it takes to try to get donors who are inappropriately on that list because the Social Security number of someone has been inaccurately entered, a name, or something like that.

And we waste a lot of time and effort and, of course, have a lot of frustrated, angry, upset donors, and once you get on this list, it is extremely difficult to get you off and/or to get the information in there correctly.

DR. MALLOY: There is another aspect that you must have in California as we do in Florida, transient residents who are there part time, and there is just no way you can have a reasonable registry that will do what you need to do.

DR. HOLLAND: Yeah, that's correct.

DR. SAYERS: In Texas the state's role is passive in that we have certain reporting responsibilities, but there's no to and fro in terms of

donor deferral.

DR. TABOR: I'm Ed Tabor from the Food and Drug Administration.

I have a question that's a sort of follow-on to the comments about Social Security numbers and inaccuracies. Ms. Norrell said that you ask for the Social Security number, and if they have an ID card with it on it, you look at it, but otherwise you just ask them. You're relying on their remembering it accurately and stating it accurately.

In Maryland within the last year or two, legislation was passed disassociating Social Security numbers from the driver's licenses. So while you were talking I looked in my wallet. My Social Security number is not on my driver's license. In fact, I have no IDs despite a wallet full of IDs with a Social Security number except for a government ID card. So I assume that most people do not have an ID card with a Social Security number, although I could be mistaken.

Dr. Sayers showed some data resulting from the Dallas-Fort Worth merger about false duplicates in the two deferral registries, in the two sort of twin cities, and doing the rough arithmetic in my head, it looked like about one in 5,000 false duplicates among the donors for the two cities combined.

And unless I misunderstood him, they could not differentiate these false duplicates solely on the basis of Social Security numbers, which suggests to me that there is up to a one in 5,000 error rate in the entry of Social Security numbers or in the memory of the individual giving their Social Security numbers.

I wonder, first of all, for Mr. Norrell how many donors are accepted without written proof of a Social Security number, and to the panel, does anyone know of studies regarding how many Social Security numbers, if you ask the man on the street for his Social Security number, are inaccurate or how many are inaccurate on donors who are subsequently found to test positive for transmissible disease?

MS. NORRELL: Well, a lot of responses to that. We did a study several years ago about how many people would actually bring an ID with them that had a Social Security number or some other positive identification, and we at that time found that we would lose approximately four percent of our total donor --

DR. TABOR: Four percent?

MS. NORRELL: Four percent if we would not allow them to donate without some form of presenting identification. At that point in time we felt that we couldn't -- we would not be able to provide our

customers with the blood that they needed if we activated that.

We do know that donors sometimes forget their Social Security number. If, when we ask the donor for their Social Security number and we enter it into the computer, if they are a potential match in the computer, then we have to ask the computer prompts us to reenter that number. So the donor would have to tell us that number again.

So if they're giving us an incorrect number or they're not sure of it, it will not allow us to go further, and we would discontinue the process.

Also this is why pre-check is not our check of record. In fact, the check of record against our deferral register is back at the center where it's round through Soundex (phonetic), you know, and lots of other criteria, not just Social Security number.

DR. SAYERS: You know, it's true in that donors have lapses when it comes to recalling their Social Security number, and since this merger, we've insisted that a Social Security number is presented at the time of registration so that a donor cannot donate if he or she doesn't give their Social Security number.

What's a little peripheral to this, but also disconcerting, is the increasing number of donors

who are really loath to give their Social Security number. You know, they're concerned about privacy issues and how much of them is being revealed to this outside organization, namely, the community blood program.

So there are problems with the Social Security, not only in making sure that it's reproducible and accurately identifies the donor, but even as far as whether that donor is prepared to release it.

MS. NORRELL: Also I don't have the statistics with me right now, but it is a fact that the Social Security Administration has in the past -- I don't know about today -- issued duplicate Social Security numbers. So we're dealing with all kinds of inaccuracies

DR. TABOR: A second number to the same individual when they've lost theirs or --

MS. NORRELL: No. The same number --

DR. TABOR: The same number to two different individuals?

MS. NORRELL: -- to two different people, and we also have as, you know, we were just talking about different ports of entry of this information. The California State Health Department has provided

lots of what they would even admit to very incorrect data. And so we have now Social Security information in our system that has basically affected people with the true Social Security number.

So, agreed, Social Security number isn't the greatest identifier.

MR. ROBINSON: You might be entertained to visit the Social Security Web page. There's actually a story on the Social Security Web page about sample Social Security cards that were included in wallets that were sold back in the early '50s, and people adopted the sample number there, and you know, there were thousands of people using that sample number.

DR. MALLOY: And occasionally a spouse will use their spouse's Social Security number, too.

MR. ROBINSON: One other comment I wanted to make sort of in relation to that is just two days ago in the Wall Street Journal there was an article about computerized face recognition, which leads into the whole issue of biometrics, which to me seems to be a reasonable answer to the dilemma, but if people are resisting giving their Social Security number, imagine their resistance to biometrics.

DR. HALEY: Rebecca Haley of the American Red Cross.

Mine are not global questions. They're tiny points of clarification.

Ms. Norrell, do you plan to put autologous donors in the DDR? You said that it's now only allogeneic donors.

MS. NORRELL: this is what my comments were strictly related to pre-check, and we don't intend to pre-check autologous donors, but in fact, if an autologous donor does have a test result or health history information that would permanently disqualify them as an allogeneic blood donor, they would go into the national DDR, but they're not on pre-check because their frequency of donation and their ability to donate is really structured by their physician.

DR. HALEY: And a point of clarification for Dr. Sayers. Do you intend to put the hemoglobin and blood pressure deferrals in the DDR since you said you may have as many as 20 percent in the DDR?

DR. SAYERS: No, individuals who are temporarily deferred do appear on the donor deferral registry. So what I said must have been spoken clumsily if there was a misunderstanding there.

DR. HALEY: Thank you.

DR. SHAPIRO: Shapiro on Life Source (phonetic) ITSM.

I want to confirm Dr. Sayers' experience in merging two large donor databases in a region. In May of 1998, Life Source merged a database with United Blood Services, Chicago, and we experienced not unexpectedly a large overlap in donors that had been eligible at Life Source were ineligible at UBS, Chicago and vice versa.

And we started with the very painful process of notifying donors who did not meet eligibility criteria for Life Source and had to tell them that they were no longer eligible since this database merger, but we felt for ethical reasons that we should allow the donors to be able to obtain their donor records from UBS, and we agreed to review them. We had to have confidentiality or release of medical information, release from United Blood Services.

It's been a very time consuming process, and I know it's been over a year and a half and we are still in the middle of doing probably close to 600 donors.

The reason we're doing this, besides the ethical reasons, is we have now acquired post donation information about donors for which we've collected units and released units over a period of time, and we have no idea because of the confidential nature of the

information what was transferred, you know, what it relates to. So we also have like a regulatory obligation to do this.

So, again, I want to say what our experience has been. In many cases some of the donors have test results that were not reproducible at Life Source. They've gone from one hit to two hits by virtue of, you know, hits in different areas for core and HTLV, and many of them have been deferrals that no longer apply, ALT deferrals, medical deferrals that are not consonant with our medical deferral eligibility criteria.

So we have been able to reinstate many of the donors, but it's a very time consuming process, and the donors went into this thinking, you know, they're very happy and grateful that we will look into this, but the time delay has taken a long time. So there's been a lot of donors that have been disappointed about how long it's taking.

So, again, I want to reiterate that since it's been a long time that we've been deferring donors for a number of different reasons, some of which no longer county, you k now, unless you're very selective of what you would put in there, and even if you are selective, you know, over time our criteria does change

as we have more and more knowledge.

It's a very dangerous process when you have to look to the future when you're doing this.

DR. KLEINMAN: Hi. Steve Kleinman from UBC.

I have two questions, and they're actually really directed at the FDA, I think, more than the panelists, and the first one is since the FDA is in some form regulating donor deferral registries, don't you think it would be a good idea to specify what criteria require a person's entry into a donor deferral registry?

Because I think we have great variability in registries, and it seems like the most basic regulatory function to say these are the things that get you on a registry, and these are the ones that don't. So I know that wasn't the subject of the discussion today, but I'd like to hear if that's part of the long range plan.

DR. FENNER: Yes, it is, and in fact, we're in discussions or arguments or discussions right now --

(Laughter.)

DR. FENNER: -- concerning that very topic.

DR. KLEINMAN: Thank you.

And my second question really comes from

previous comments that were made, and also having worked in the State of California and experienced that deferral registry.

Again, it's sort of a ridiculous question in a way, but doesn't the FDA have -- as it can go in and inspect blood banks, and if a blood bank had a deferral registry with the quality of the State of California registry it would cite them and probably stop them from operating. Can't the FDA exercise some control over, you know, what is clearly in inept and inadequate system?

I know there are state and federal jurisdictional problems, but I mean, the state is regulating the blood supply in the State of California with a system that doesn't work, and it seems to me that the FDA should have some kind of clout and have a responsibility to get -- I mean, the state won't clean up its act. They're under resourced. They're dramatically under resources in that registry.

So I throw that out for consideration.

DR. FENNER: It's a good point. I don't know that our jurisdiction would cover intrastate DDRs or whatever, but it's certainly a point.

DR. KLEINMAN: Right. It just seems like it's a system that everybody knows doesn't work, and as

Paul said, there's really no recourse to make it work, and we don't tolerate that in the rest of the blood system.

DR. BIANCO: Hi. I'm Celso Bianco, New York Blood Center.

I don't have a question. I have a comment that is actually a little story.

In about 1969, the New York City Department of Health decided to create through the blood banking community, in conjunction with the blood banking community a deferral registry for hepatitis in the City of New York, and the sources of data were obviously collections made by blood centers and hospitals.

And in addition to that, all clinical labs were required to report results of any hepatitis related test to the New York City Department of Health. Obviously there was no real control. Social Security was not required. It was just name, address. Date of birth was not required, and the list kept growing, and the city Department of Health kept passing to us thicker and thicker books until we got into the computer era and reel-to-reel tapes were exchanged between large institutions.

In the early '90s, we could not collect blood from anybody called John Smith or Dick Taylor or

Jose Rodriguez because they were all deferred.

(Laughter.)

DR. BIANCO: We were very lucky in having the community work together with the New York City Department of Health and the New York State Department of Health, and I just want to tell you that in 1994, the list was eliminated, and we do not have a New York City or New York State deferral registry.

MR. MIETZNER: George Mietzner, Mayo Clinic, Rochester.

Got a quick question. One of the things that we're throwing around in our management meeting is in the windows we are going to have to go to a system to positively identify our donors. In the conversations I'm getting from today, Social Security isn't the greatest number.

Currently we use their Mayo Clinic ID number. In order to donate in our centers you have to have that. It's sort of a small, self-regulation process that we're looking at abandoning to go to that positive ID marker.

Is there anything out there that -- I would have thought the Social Security number is a good one, but is there anything that we can look at that could possibly lead us to that positive ID?

DR. MALLOY: Well, I heard someone here say the word, and it came up earlier. We actually have begun to look at -- we first started to look at the fingerprints because they're available for check cashing, and the technology is fairly available. Most grocery stores have it, I believe, and it's inexpensive.

There apparently are even better biometric markers that can be done fairly unobtrusively. We aren't doing this yet, but it's on our list of things to look at. And you don't have to remember it. It comes with you.

(Laughter.)

MS. NORRELL: So we also have looked into fingerprint scans and retinal eye scans, and we're actually looking now more towards, because the technology has gone so far with Web based possibilities; we're really looking more at things on line like photo IDs.

We haven't made any decisions, but those are the technologies that we're looking at.

DR. FENNER: One question I have is the FDA at this point is considering proposing that we require an identification from a donor with a photo on it and an address. Does anybody have any experience with

that?

DR. MALLOY: I wouldn't inflict my driver's license photo on you if I could avoid it.

MR. ROBINSON: In the source plasma industry, we have addressed that somewhat because by regulation a photo is required, but what we have found is that in some instances, as was pointed out earlier, if your Social Security number is not on your driver's license, there's no link between the photo of the person you've taken a photo of and the ID that they present as well. So there's still a disconnect there.

DR. FENNER: Our link would not be with the Social Security number, but only with some sort of positive identification with a photo on it.

DR. HOLLAND: Paul Holland, Sacramento.

In our blood center, we require a photo ID to donate blood. The main reason we do is to make sure we don't take under age donors, and actually most students have driver's licenses these days. So it's not a problem, but I think it's one way to insure you at least have the right person.

So we do require a photo ID of all donors. If they don't have it, we don't take them.

DR. FENNER: Do you have any data that indicate how many donors you have to turn away because

they don't have a photo ID?

DR. HOLLAND: I'm sure we do. I can check for you. I don't know.

DR. FENNER: Okay.

DR. HOLLAND: But we wouldn't take them without a photo ID. I think it would be inappropriate.

But as was said earlier, most people do not have anything with their Social Security number on it. So we really rely on people's correct giving it to us because nothing I have has my Social Security number on it.

MS. NORRELL: And when you implemented the requirement for a photo ID, did you phase that in with a lot of communication to the donor base so that they -- you didn't have a period of time where you lost donors because they weren't prepared for what you were going to --

DR. HOLLAND: Well, we phased it in in the sense, yes, we certainly had our donor recruitment meetings and all the pre-up front donor communications by donor recruitment warn that it was going to happen, but it was implemented and very abruptly, and if you didn't have it, you couldn't donate.

DR. SAYERS: You know, I'd make a plea for trying to get the system that is in common practice to

work, namely, the Social Security number because I'm worried the more you ask donors up front as identifiers, the more you leave him or her with the sense that you're disputing the information that's being provided, and goodness knows, we set the stage for the donor being left with that expectation after we've gone through all of the questions that we've gone through for the umpteenth time that year.

You know, I do believe in our experience that we can get the Social Security number to work. You know, I agree with Paul that there might be other reasons to require a photo, but I think a Social Security number is a donor identifier that we can get to work.

DR. HOLLAND: I mean, you must use the system. It's the one common number, and with our transient society, it would be the one number that people would bring with them.

DR. BIANCO: Celso Bianco again.

At New York Blood Center, we have an experience that is very similar to that that Paul reported. We require a photo ID, and we require that the donors give us a Social Security number.

And actually the three identifiers that we use are the name, the Social Security number, the date

of birth, and that's the algorithm that I think many of us utilize.

Yes, there is a substantial number -- there are many donors that do not either have an ID or do not want to give us a Social Security number that we do not collect. In the early days this number was up to five percent in many of our drives.

There is one special category that I'd like to remind all of us of. I understand that FDA is looking for formulas, but we cannot be extremely rigid, particularly. For instance, in New York City, kits cannot have driver's licenses until 18, the age of 18. So most of the high school kids do not have a photo ID of any kind.

PARTICIPANT: A student ID.

DR. BIANCO: They do not have photos in New York City, the kids in high schools. Colleges, yes.

And so what we have had is to create some alternative systems because we want kids from high schools to donate. That's where they learn how to donate blood. That's where they understand the things.

So some of the alternatives that we have in our SOPs, for instance, we have the class teacher recognizing each one of the students at the time of the registration and confirmation of their identities.

So I would ask FDA as you consider those measures to consider alternative forms of identification to deal with this particular case.

Thank you.

DR. SAYERS: Celso, how much deferral do you experience attributable to the donor failing to bring in a photograph?

DR. BIANCO: Now after several years and a lot of the instruction, a lot of pieces of paper, that is the same way that every piece of paper -- let's say if you have hepatitis before the age of -- after the age of 11, you cannot donate. They all say that you have to bring a photo ID, and the Social Security. So now I would say it is about one in 1,000.

DR. SAYERS: Are the likenesses ever disputed?

DR. BIANCO: The likenesses? No, but our historians have the authority, that is, if they doubt the information about the donor, not to accept the donor, to defer the donor on the spot, or if they don't feel comfortable doing that, to note in registration form so that the registration will be made, the unit will be collected, but it will be deferred and will be discarded, but those are rare, very rare events.

DR. FORREST: I'm John Forrest with Alpha

Therapeutic Corporation.

My experience in source plasma industry, and I think almost all of us now require a photo ID and Social Security number from the donors; not all of us require proof of Social Security number, but it seems that the donors do get used to the system, and after the first -- probably after the first year of requiring photo ID, it seems like almost any plasma donor center in the country the person shows up with a photo ID knowing they can't donate without it.

Social Security number, very difficult, even more difficult to apply because there are resident aliens in this country who do not have Social Security numbers. They have other numbers to identify them, and those don't necessarily work in a Social Security number system.

I believe the current resident alien number system is one letter and nine digits. So it requires ten spaces instead of nine, and it won't work in a lot of computer systems. So that's something that needs to be considered also.

DR. FENNER: Thank you.

How long are we breaking?

MS. CALLAGHAN: Okay. I think we can take a break and be back here at 11.

(Whereupon, the foregoing matter went off the record at 10:40 a.m. and went back on the record at 11:01 a.m.)

MS. CALLAGHAN: If everybody could sit down, we could start with the next section.

I have a couple more housekeeping items to discuss. Number one, they have just arrived. So please make sure you pick up your little pen that's outside on the table. They are for you to put into your millennium time capsules.

No, please. Joe and I went through all sorts of things to get these pens. So -- oh, well. Enough said. When we both get canned, you'll know why.

And, number two, the speakers who haven't provided me with copies of their slides and presentations, could they please give them to me in case people request them?

Okay. Now on our second part of volume of blood that can be collected. I'd like to introduce our moderator, Dr. Ellen Lazarus. She's a medical officer in the Department of Hematology in CBER.

DR. LAZARUS: Thank you, Elizabeth.

By way of introduction to the second session on donor blood volume, I will present a brief overview of the Food and Drug Administration policies

and guidelines pertaining to donor blood volume and blood product collection volumes.

As you will see, most of these policies and guidelines rely on body weight as a surrogate for total blood volume suitable for on-the-spot determination of a healthy donor's ability to tolerate the extent and duration of extra corporeal volume associated with a given donation procedure. Alternative approaches to donor blood volume assessment will be presented by other speakers during this session.

I will begin with a summary of current FDA policy regarding body weight requirements for whole blood and source plasma donors. As stated in the CFR Section 640.3(b), general donor qualifications, "a person may not serve as a source of whole blood more often than once in eight weeks, and in addition, donors shall be in good health," as indicated by several listed physical assessment and health history parameters.

Currently an explicit requirement for a minimum donor weight for whole blood donors is not included in this list. However, as a practical point, CBER has not to date approved protocols for the routine collection of whole blood from donors weighing less than 110 pounds.

In contrast, the health assessment parameters to qualify a source plasma donor, as listed in CFR Section 640.3 -- .63(c), include the requirement that source plasma donors shall weight 110 pounds at least.

So what is a unit? This simple question belies the complexity of the issue in this era of designer blood products, which some of the speakers in this session will address.

A unit is defined in the CFR Part 606, current GMP for blood and blood components, as the volume of blood or one of its components in a suitable volume of anticoagulant obtained from a single collection of blood from one donor.

Specifications for blood containers further define the features of the unit. Regarding anticoagulant content of blood containers in 21 CFR 640.4(c), specifies that the amount of anticoagulant required for the quantity of blood to be collected shall be in the blood container when it is sterilized.

In practice most approved blood bags contain an appropriate amount of anticoagulant to college 450 or 500 milliliters, plus or minus ten percent, to give you a range of 405 to 550 milliliters of whole blood.

Also as a practical point, CBER has not approved any product license supplement for routine low volume collections, and similarly CBER has not at least recently licensed an anticoagulant adjusted blood product, such as a product -- this sort of product wouldn't be in compliance with 640.4(c), and also we would be concerned about the accuracy of the calculations and the manipulations that would need to be done.

Currently proposals are under consideration as part of the FDA's blood initiative to revise the requirements for donors of human blood and blood components. One proposal would require that a donor must weigh a minimum of 110 pounds or 50 kilograms to participate in a collection program for blood and blood components, including source plasma.

Another proposal under consideration is to establish a specific whole blood collection volume based on the capacity of approved blood containers, for example, 450 or 500 mLs, plus or minus ten percent.

Possible exceptions to these requirements have been discussed for a number of unusual circumstances, non-routine collections, including physician approval of a donor weighing less than 50 kilograms for a directed donation or other special

circumstance, and in this scenario, proportionately less volume would be collected down to a lower limit, say, 300 mLs, and the plasma and platelets would be discarded.

Another exceptional situation is inadvertent collection of a low volume unit usually due to technical problems during the phlebotomy that prevent full collection. At least one license supplement of which I'm aware was approved in the past to allow use of such units.

So the rationale for establishing donor weight and collection volume requirements include several considerations in addition to the obvious concern about donor safety.

In addition, it's desirable to provide consistent donor suitability requirements for blood and blood components whether they're intended for transfusion or further manufacture. It is desirable to attempt to standardize product dose at least within a defined range, and of course, to reduce transfusion recipient exposures by limiting production of low volume units.

And then finally, it's necessary, of course, to maintain a proper blood to anticoagulant ratio.

However, there are disadvantages of the donor weight requirements under consideration. Specifically, minimum weight requirements may exclude some female donors or donors of some ethnic groups, and this could potentially exacerbate regional blood shortages.

In addition, to be discussed a little bit later in my presentation, additional weight requirements for doubt unit apheresis red blood cell donors may conflict with specific donor selection algorithms used in some collection devices.

Some additional policies that I will review involved plasma pheresis. The requirements for infrequent plasma pheresis donors I've lifted out of a revision of a previous FDA memorandum, and this revision is dated March 10, 1995, and in this document infrequent plasma pheresis is defined as every four weeks or less frequently.

Plasma, which includes source plasma and FFP, may be collected every four weeks maximally from donors who meet criteria for whole blood donation and weigh at least 110 pounds. The SOPs at the centers should insure that these donors have not been participating in other apheresis programs and, therefore, to insure adherence to the frequency limits,

and the maximal allowable annual volume would be 12 liters, except for donors weighing greater than 175 pounds, where the maximum would be 14.4 liters.

In a proposed rule published in the Federal Register, Volume 64, Number 160, there are revisions to requirements applicable to blood, blood components and source plasma, and I've just summarized on this slide the plasma pheresis changes. In this proposed rule, 21 CFR 640.65(b) would be modified to clarify the application of the blood volume collection limits established there to manual apheresis procedures, and then a section would be added to address automated plasma pheresis, and a section would include frequency of collection that would basically be consistent with the above sections.

And then in addition, this added section would mention the volume of plasma collected, and it would be consistent with volumes approved for each device and recommendations in the FDA memorandum, November 4, 1992, about volume limits for automated collection of source plasma.

In my next slide, I just reproduced the simplified nomogram that was published at that time in 1992, and there are, of course, some caveats to the use of this nomogram. One is that this isn't the only

nomogram that can be used, but rather this is just an example of a nomogram which can be used at a center, and the point being only one nomogram or one system should be used at each center, as opposed to choosing different nomograms depending on the donor size or the types of products that needed to be collected at a particular time.

In addition, this nomogram, the numbers here apply only when the anticoagulant used is four percent sodium citrate administered at a rate which will yield a one to 16 ratio of anticoagulant to anticoagulated blood.

And then as a final point, this was pointed out to me by a colleague who reviewed my slide. If you do the calculations volume using specific gravity, the numbers aren't quite the same, and the difference will be give or take a couple mLs, and we felt that that wasn't a critical difference.

Okay. Moving to platelets pheresis, the platelet pheresis donor suitability criteria are listed in 640.21(c), and they basically say these criteria are described in a license application or supplement to a product license.

Regarding volume, the revised guideline for the collection of platelets pheresis, which was

published in October 1988, states that the total volume excluding anticoagulant of all blood products retained per procedure should not exceed 500 mLs or 600 mLs for donors weighing greater than 175 pounds.

But as many of you probably know, device manufacturers have received clearance for larger total volumes subsequent to the publication of this guideline.

Finally, addressing apheresis red cells, donors should meet all FDA criteria for standard allogeneic whole blood donation. However, in the draft guidance additional criteria for allogeneic double unit red cell donors were included, specifically weight and height.

However, based on responses to that draft guidance, these are expected to be revised and, in fact, eliminated potentially.

In addition, the draft guidance includes the specification for a predetermined target volume of each red cell unit prior to collection be stated in the operator's manual, and this volume would be based on gender, weight, hematocrit and the type of procedure selected.

So in summary, the FDA position on donor blood volume and blood product collection, it's a goal

that we share with everyone here. The objective is to determine a safe blood product collection volume based on donor blood volume estimates, and it's important to develop collection protocols that will maximize the benefit from each volunteer donation and without compromising donor safety.

And finally, it would be desirable to standardize a product dose in order to achieve a predictable therapeutic effect and, of course, limit unnecessary exposures.

So now I would like to invite our next speaker, Dr. John Forrest. He is the manager of regulatory affairs at Alpha Therapeutics, and he is representing ABRA.

He will be presenting data on the volume of product collected in relation to body mass.

DR. FORREST: Well, good morning, everybody. Elizabeth, I'd like to thank you for inviting me to speak at this workshop. I'm glad we're having it a year later, but we still get to have it.

I've sort of been asked to present a somewhat historical view of the evolution of the source plasma collection nomogram and how we got to the one that was just presented going back through a history of where we started and why we ended up with that

simplified three volume nomogram.

Next slide.

As a review, the current CFR is still manual pheresis oriented and specifies essentially the volume limits that were done with the old two bag source plasma/plasma pheresis procedure where you would withdraw one bag of blood, centrifuge it, remove the plasma, reinfuse the cells and repeat the process a second time on a donation.

And so essentially it was two bags at one donation and four bags in any seven day period. That's been that way since the '70s, whenever this regulation was published. It predates me and my involvement in this industry.

In the late '80s, CBER did issue a guidance memorandum that said 48 hours. Two calendar days can be construed as 48 hours because there were issues like, well, what if the donor donates at seven o'clock on Monday night and seven o'clock on Wednesday morning. That's not 48 hours. Is that acceptable?

Thankfully we all got away from having to keep track of the hours and minutes of the day as far as tracking donations.

Next slide.

However, automated plasma pheresis really

came in about 1984 and '85. People were starting to use it in a small degree. We had some early challenges in that even though the Center for Devices had licensed the Hemonetics PCS in the at that time HemoScience auto pheresis, to collect source plasma CBER was challenging the industry that was collecting it to prove that the material coming out of the machine really was source plasma, and that it was essentially identical to what we had been collecting in the manual pheresis system.

So we had to do some pilots and trials and do some detailed analysis of the output of the machine to show that the raw material that would be going into our final product manufacture was identical to what we had always done.

Since the early '90s, widespread use of auto pheresis. I'm not sure that anybody doing routine source plasma collection has used manual pheresis in at least a couple of years. We still do have the major device manufacturers, Hemonetics and now Fenwal.

They had some problems. Each manufacturer approached nomograms a different way. Hemonetics did a more complicated nomogram, you know, using body mass indications, height, weight, hematocrit, all of that rolling together. I'll touch on it a little more.

Fenwal's was a little more simple approach,

but still rather complicated when you think back to manual pheresis and you had one decision point. Did this person weigh 175 pounds or not? If they did, they got the larger blood bag, and it became a lot more complicated when you do that. You get a lot more errors in collecting the appropriate volume.

Okay. Now, the Hemonetics nomogram actually started with you had to pick one for whether you had a male or female donor, and then you had to cross-reference donor weight and donor height. Weight was in ten pound increments. Height was in two pound (sic) increments, and you followed those down and you got code letters, and the best way to describe the way it appeared was like a pantyhose chart of these little jig-jag marks so that there's black and there's white, and they all have different letters associated with them. Only there were six letters on each chart, six on the male and six on the female, with not 100 percent overlap. So there were really seven different letter categories you could determine.

Then you went to a different chart, and you took that letter and the hematocrit, and you had to follow those two down to actually come up with a volume to program in the machine, and you ended up with a volume range of for females 470 to 850 grams, and for

males from 530 to 850 grams of plasma that could be collected.

But given all those different variables, obviously there are many opportunities for error in programming the machine.

On top of that, the early versions of the machine programming left the volume to be collected set at whatever it had been for the previous donor. So if you are pheresing a 200 pound donor and the next one was 110 pounds, you obviously had an opportunity to over bleed them by about 300 mLs of plasma, 300 grams of plasma.

The other nomogram, the one that became the Fenwal version, was a little simpler, but first you had to decide which percentage of anticoagulant you were using and know that isn't four percent sodium citrate. That's the at a six percent or one to 16 ratio, and there were other charts because the machine was used in Europe where they were using ACD or CPD with source plasma instead of sodium citrate. So you had to figure out whether you were doing a six percent, eight percent, or I think 12 percent ratio of anticoagulant in anticoagulated whole blood, then pick target volumes based on weight increments and programmed it in.

To add to the confusion, there were

actually centers using both machines. The Fenwal approach was in mLs in plasma instead of grams of plasma. So you could have to do transpositions and have charts that told you that if, you know, this many grams equal this many mLs so that you could actually figure out what you were ending up with.

Okay. Obviously we all felt as an industry there were a few problems with this set-up. Obviously the multiple steps, a lot of chances for errors in programming, both under collections and over collections. Obviously the over collections is a donor safety issue. The under collection, more of an issue of economics. I mean that's essentially lost money and lost raw material going into the plasma derivative products.

And the actual nomograms that were approved by the manufacturers were fairly conservative in their approach, and especially on the heavier weight donors with low hematocrits, we are actually losing volume compared to the manual system, sometimes fairly significantly, like maybe 80 mLs of plasma less than getting with the manual system.

So we began to explore other options of how to both decrease errors and increase volume, and in November 1991, Premier Bioresources, Inc., which no

longer exists, but I was responsible head there at that time, we submitted a proposed three volume nomogram to the FDA trying to simplify and eliminate errors and also address the volume concern.

That was actually approved in February '92, a fairly quick turnaround time on it, and then as it was referred to already in November of '92, that became a general guidance to the entire industry, saying that you could apply this nomogram, and they made it universal to any automated device used to collect source plasma.

I also touch on how we came up with that new nomogram. Surprisingly it was all paper argument and no clinical data involved, which was nice. It got it done a lot faster.

The first thing we did was actually get a snapshot of who our donors were, what our donors were. We went to all our centers. At that time I believe we had 22 different collection centers around the country and documented donor weights for every donor who came in in a two day period so we'd make sure we didn't count any donor twice.

We also tracked hematocrits for all those donors, and then analyzed the data, and I'll show you just for the weight what we came up with in just a

minute, but then we figured out like average weights, average hematocrit of our donors.

I did a bunch of research using different tables, and you know, anybody who looks through the medical literature can see that everybody has their own way of figuring out how to calculate blood volume based on body mass.

There's tons of different numbers. Selecting several and sort of averaging them out, I came out with one that was approximately 35.4 mLs per pound of lean body mass, and with the 44 hematocrit, which was our average hematocrit, that came out to 19.8 mLs of plasma per pound, lean body mass.

So then I did comparisons comparing out of that percentage of total plasma volume, what we would have taken out in the old manual system, what the current nomogram took out, and what our proposed nomogram would withdraw as a percentage of that volume.

I also did some calculations which I'll show you based on what I am sort of referring to as real body mass as opposed to lean body mass. We don't tend to have too many donors who are coming in here with, you know, four percent total body fat like some world class athlete would to try to see what the impact would be on normal people that are five feet, eight and

weigh 175 pounds, 200 pounds, whatever the different weights are.

Next slide.

Weight breakdown. I've always found this a little interesting, but we always find in source plasma, and I've done this several times, that there's not a significant difference in the weight of our male donors and female donors. Even though most of them are male donors, here it was 168 pound average and for the females, 159.

I've done snapshots at other times that have actually been closer to where there's only about a pound difference in the weight between the male and female donors.

Hematocrits do vary more, and I think that's why we get a 44 average. I don't have a chart for it. Unfortunately I didn't keep all of that data from that time period, and like I said, Premier doesn't exist anymore. They've been bought out by another company, and I'm working for Alpha now instead of that company. So some of this data is probably lost forever.

But the female hematocrits predominantly ran I would say from 38 to 44 and the male crits. more like 42 to 48, was probably more of a central range for

those, but weighted them together, we end up with the 44 hematocrit for our donor population.

This was just simplifying the data that was submitted to FDA to show what the actual impact was comparing what was done in manual pheresis and what would be done with what is now the current simplified nomogram.

We stuck with the 110 pounds, I guess, just because we'd always used it. It was in the CFR, and we didn't want to get into those kind of debates of whether that 110 pound minimum could be withdrawn given that there is auto pheresis and much more specific programmable weights.

I left the 175 pound category in there essentially for the same reason. There was a lot of history associated with that because source plasma had always made a break to go into the larger collection volume at 175.

You can see that the maximum withdrawn is still in the 110 pound donors, and essentially I maintained it to be identical with the manual pheresis so that we -- you know, I felt that that was a fairly significant amount of volume to withdraw in plasma and didn't want to push much past that.

You see now though that at 150 pounds --

and that's where the next category, the new category essentially slotted in, from 150 to 175 pounds, that we pushed that back up somewhat to try to boost the percentage withdrawn, not quite as high as we were doing in, say, the 110 pound donors, but more approximating that 120, 130, and 140 pound categories into 150, 160, 170.

And then at 175, we added yet another little boost, but it's not a whole lot different than what we are getting in the manual pheresis.

Now, comparing real body mass, and what I used for that, I found a couple of references back in 1991 when I was putting this together that said that a person with an obese body build had about one percent less blood volume for weight than a person with a lean body mass. So I've actually just reduced that 35.4 mLs per pound by one percent, which drops it down to 35 mLs per pound.

And you can see that it's almost a negligible impact on the plasma side. It drops it by .2 mLs per pound as far as what the total plasma volume is.

And, once again, this is all based -- the hematocrits are 44, but you see it just jumps from 28.7 to 29.0 as the amount withdrawn for somebody who's not

a lean body mass.

This is what was actually submitted. These numbers include the anticoagulant. If you subtract that out, the numbers were 625, 750, and 800 mLs of plasma, and I say mLs because at that time we were using the Fenwal machine exclusively. So we were used to working in milliliters and not grams. The FDA presentation gave it both ways.

As part of the guidance document from CBER publishing the nomogram, they did allow people to immediately implement it. This was back in the days before this annual update in things to your license amendment where pretty much everything in source plasma was requiring preapproval before you did it, but this memorandum did allow us to implement this right away or allowed the industry to implement it right away.

They did request that each firm as they implemented this, each license holder, monitor the first 1,000 procedures and report any donor adverse events to CBER so they could do an analysis to make sure that nobody was seeing an increase in adverse events in the donors.

My experience at PBI and what I remember anecdotally from the others is none of us saw any increase of any degree related to volume related or at

all in adverse events, and with automated phereses the adverse events had dropped to almost nothing anyway compared to the old manual pheresis days where we did have a more significant change.

There were problems comparing adverse event rates. Different firms use normal saline as a volume replacement in serial plasma pheresis. At Alpha right now we give all new donors 500 mLs of normal saline at the end of their first donation, and we give it to females on every donation. That was in place before I got there. I'm not sure what all was involved in their making the decision to approach it that way.

At PBI we use saline volume replacement at every donation. There are other companies out there that don't use it at all, and the adverse event rates don't really seem to vary to any significant degree, like tenths of a percentage point.

I think part of it is just with the automated pheresis, the volume withdrawal is slow enough that the normal physiological processes are starting to shift fluid around during the 45 minutes to an hour that the donation takes. So by the time the donor gets up, they haven't really -- they've already started pulling some of that third space fluid back into their vascular system.

That's all I have. Thank you.

DR. LAZARUS: I would like to invite our next speaker to the podium. Her name is Linda Papenfus. She is representing ABC, and she's the Director of Quality Assurance and Education at the Blood Centers of the Pacific.

MS. PAPENFUS: Good morning. Yeah, it is still morning, especially for me.

I have to tell you that I was expecting snow. I wanted snow for Christmas. So I came all the way from San Francisco and the weather is as nice here as it was back home.

A lot of what I'm going to go over in your slides I will tell you if you're looking at the slides in advance, that I am going to skip some because they've already been covered by Ellen or by John and they'll be covered by somebody who's coming after I am. So I don't want to confuse you, and I talk fast. So I promise not to go too fast so we can keep up with each other.

Go ahead.

What I'm going to talk about today a little bit is a little bit about the rules. I'm not going to really say much more about that. You've already heard them.

I'll say a few things. What does and can go wrong with volume and frequency in donors? What's happening now?

Part of my role, and I should make the disclaimer that I'm here at the invitation of Elizabeth -- thank you -- but also ABC, but like everyone else before me has said, I'm not representing ABC's opinions. I was asked to gather the data for them and talk, but I did poll a lot of ABC centers. That's where I'm getting my information to share with you today.

I want to talk about what's happening out there with those centers, with the ABC centers. What are their questions and concerns and what information they wanted me to bring back to this meeting to be part of the information to be shared, and also where do we go next.

Obviously underneath all of this is donor safety in regard to volume and frequency and product safety and quality, and also retention of the donors. It was interesting, some of the comments that I got throughout gathering data, concerns where donors were angered, turned off. I heard that early this morning about donors getting mad when they're told something twice and so they don't come back or they're angry when

they come back again.

I found that also in talking with the centers throughout gathering my information and presentation.

The next couple of slides talk about rules. Go on.

This slide, just to let you know, this wasn't to imply that the FDA didn't have an opinion or that they didn't have something to put in there. This is one of those modern technologies. One program wasn't compatible with the other in software, and it wouldn't let me change my slides. So there is a hole there.

But had the point of these slides to show you that the AABB and the FDA are very similar, in fact, the same right down the line. This year with the 19th edition of the Standards, the AABB put the 10.5 milliliters per kilogram of body weight in as a standard, and that gave us a little bit more leeway in terms of volumes for donors.

Go on.

The next sort, I'm not going to go with this. I just wanted to point it out. If you have not used the AABB Standard Source, it's new this year. It's an excellent document, a lot of good information,

and we use it a lot, and it also goes into a little bit of information to explain the 450 and 500 mL and also 10.5 milliliters per kilogram of body weight. So I recommend it.

And it's in your handout if you want to look at this particular slide.

Rules as far as plasma and red cell loss during apheresis, to red cell pheresis. One of the things that Ellen didn't cover was red cell loss during apheresis. If it's greater than 200 mL, the donor must be deferred for eight weeks, and there has to be a cumulative record kept. So that is something that we looked at for volume, especially when we've got donors who are doing both pheresis and whole blood.

As far as platelet -- go on, yeah -- platelets, she's covered all these things. Probably the most important with the volume is also the frequency, and this is one that you'll hear me talk about when we get to the questions and concerns on what's really happening.

A lot of comments on this one is all I can say for right now.

Next slide, please.

Plasma, John's already covered this, and I won't say anything more about that one.

One rule I'm going to add real quickly because it does have a little bit of play in my presentation, and that is about errors and accidents and what do we call errors and accidents, and the FDA or the CFR 606 and 211.92 both talk about investigation of incidents of discrepancy, and that there must be a written record, and these will play into a little bit more of the information I'm going to share with you.

You can go on actually to the next. Keep going.

And what can go wrong? Well, this last November Sharon O'Callaghan (phonetic), not to be confused with Elizabeth Callaghan, gave a great presentation at AABB in San Francisco about reportable errors and accidents, and she and I had quite a good conversation about errors and accidents related to volume and frequency of donation.

And these are points, in fact, from her slides or her presentation in San Francisco, and she talked about errors and accidents as being related to the manufacturing process, affecting the safety, purity and potency of the product. What's the intended use of the product, and was the product made available for distribution?

These are questions that should be going

through our heads as industry folks when we have a problem in our centers or in our institutions.

She also went on to give a couple of examples. These are reportable examples. If the volume maximum exceeded and the product was distributed, this was a reportable error. If the anticoagulant to blood ratio was incorrect, she and I had a discussion one day about if it's incorrect, if it's too much blood, for instance, and the blood product is modified in some way -- is that me beeping? Thank you -- is it acceptable to use that product?

Nonreportable examples -- next one -- these are things that were not reportable. This goes back from '96, '97, '98, and '99 FDA reportable errors and accidents and what they found in reviewing them, and what Sharon found in reviewing them was actually not reportable, but are still being reported.

Time interval between donations not being met. It's not reportable as far as they're concerned unless, again, there's a problem with the product.

Donor did not meet criteria for blood pressure, pulse or weight. Overdrawn, but not distributed, and donor did not meet acceptance criteria for platelet count and the product was acceptable.

I found this very interesting because my

own institution has gone through a change as to what we reported, and when I did the survey for the blood centers, I found that many of them were not using the same criteria, and they were reporting things that the FDA, in fact, has told us are no longer necessary to report.

What's happening now as far as the centers surveyed? This was probably the most interesting part. I really enjoyed doing this, and I actually am going to go on and do some more because I didn't get a chance to do as many centers as I would have liked to. I got a lot of good information though.

Collection bag size, what are they doing? What's happening as far as actual real centers and processing as far as units? Four hundred and fifty mLs, 60 percent of them are using that, 24 percent using the 500, and seven percent doing both. Those that were using both have a lot of criteria or things specified. For instance, one center would only draw what they considered smaller females and all high school students and 450s, and everyone else wanted a 500 mL bag. Other ones drew the 450 at certain mobiles. They just simply did 450 mL because they expected more lower weight donors, and that was how they kept track of them.

As far as what they considered overdraw, most of them did the usual ten percent, plus ten percent, anything over that was considered an overdraw. Other ones had very set volumes that were within that ten percent, but they weren't just ten percent, and a couple of them had set volumes that were over the ten percent, which I found interesting also. So a lot of interesting information that was out there.

As far as the whole blood volumes for autologous -- I mean homologous -- I'm sorry -- what would they do with the units? Well, 75 percent said that they would discard them if there was an overdraw. Some would sell to research. Some would wash and filter and then distribute.

This was an interesting point. Many more than ten percent acknowledged that they did wash and distribute or filter and distribute, but they no longer do that because they were concerned in the changing regulatory environment that that would be against some regulations, whether it would be state or federal, but they want to go back to doing that, and that was one of the questions that came up a lot of times, is what is the nature of -- what happens to that unit? Can it be washed and filtered and be usable?

Some just didn't know. They said that it

had never happened. I don't know about you, but I found that very hard to believe, but this was homologous.

Now, the autologous ones were a little bit different. Only 20 percent said they would discard. Many of them, 23 percent said that, no, they'd have medical review. Another 22 percent said they would look for clots. If there wasn't any clots or any visible reason not to distribute, they would distribute the unit, letting the physicians know most of the time that that's what they're distributing, an overdraw.

Some also said that they would wash and filter and distribute, again, not as much concerned because of an auto., and there was more concern that this was a product that was a little bit more special in their eyes.

As far as overdraws reportable to the FDA -- you can go on -- 52 percent said that unless it was an auto and they shifted out of their center, they would report if they thought that that was, in fact, reportable error.

Thirty-two percent said they wouldn't report; it wasn't an issue. And those that said available for distribution were five percent, which I found interesting since that's what the CFR says very

clearly that they were available for distribution. And some just didn't know, and again, some just said it never happened.

So those centers -- I actually want to go visit those centers.

The next one was frequency. This, again, was a very interesting one for me. I know that we were talking about volume and body mass today, but that all related in my mind and in my work that I do with how often does a donor come in. If the volume is affecting the donor, so is how often they come in to donate that same volume or less or more.

Time intervals not met. We mean a donor came in, presented too soon and was drawn or, I guess, in some cases not drawn, but occasionally -- 63 percent said occasionally they had a donor present. Fifteen percent said it never ever occurred, and they were adamant it never occurred, and ten percent or 25 percent -- I'm sorry -- said they did not know.

As far as those that occurred that said occasionally, 63 percent said they came in one to two days too early. Well, I mean, I think there isn't a center or a blood collection facility anywhere that doesn't have someone come in a day or two early.

Occasionally nine percent said they had

some come in less than a week, but more than a couple of days. Another nine percent said rarely over two weeks. Fifty percent didn't know; they didn't track; they didn't have a system to track.

And an interesting point. On two different centers, they told me they had an occasion where a donor came in the same day. It was really interesting because when I was chatting with Sharon O'Callaghan, she was sharing with me some of what she considered fun FDA reports, and one of them was a donor who came in to donate at a center on one day and that afternoon went to another center to donate and the next day called back with a post donation report of being fatigued and very dizzy and tired.

(Laughter.)

MS. PAPENFUS: And he called the first center, and of course my first question to Sharon was, "Well, how did he know which one to call, you know, the first or the second unit?"

And upon investigation they found out that this, in fact, donor had donated twice at two different, not the same center within a facility; two different organizations.

Another person that I chatted with on the phone while I was doing the surveys had a donor who

came back to two different centers within their own facility in the same day and was not caught, and didn't have any post donation reaction though. He was perfectly fine.

No one else admitted to any of this happening. Certainly not at my center; we haven't done someone on the same day.

Going on to what to do with those units, 66 percent said they would use them. A little bit distressing to me was that 15 percent said they would discard them, all conditions being okay, the donor being fine, all criteria being met, no issue at all. They would still discard them.

And on further questioning, because I in this day and age am having such a problem with blood shortage, I was amazed, and they said, "Well, the regulations are very clear. They have to be 56 days. So, therefore, I cannot use that unit."

And when I asked if they had talked with their local regulators or with CBER or with FDA, they said it didn't matter. That was a regulation. That was the way it was, and they couldn't use that unit.

That was a bit distressing for me knowing how short the blood supply is.

Some said medical review and some said they

didn't know.

As far as what they would report to the FDA, 31 percent said, yes, if they came back in too early and they did distribute the unit, they would report. Well, we saw earlier from Sharon's information that they don't have to report them, but they're still reporting them. So there's some information that's not getting out to everyone out, and yet 54 percent said absolutely no, they wouldn't report, and eight percent weren't sure.

Now, these don't add up to 100. Don't worry yourself, please. There are some people that just had no opinion at all, didn't want to give any response.

As far as what they would do with a unit, again, even though they would report them or not report them, they would still distribute them.

Red blood cell apheresis. Just real quickly, I'm not going to touch on this too much, except it's obviously becoming more prevalent. Twenty-five percent of the centers that I talked or spoke with are, in fact, receiving pheresis multiple units or else multiple red cell and product mixes. No one to date had any problems or had reported any issues that would have been FDA reportable.

There were some questions, of course, about the whole process and about how the regulations are going to finally turn out, but no real issues as far as the process itself.

Platelet apheresis. The majority of centers I spoke with or surveyed did, in fact, do platelet pheresis. One of the things that came to be the most interesting to me was how they decide how many donations they could do a year.

Now, the set calendar and rolling calendar, I never really thought of as a big issue, but there were some very definite people who feel very definite about January through December must be that calendar and others who feel when you're done with January you drop it off, and it's the next 12 months.

I don't know about you guys. I spent a half an hour with a chalk board with my staff, and I couldn't find a difference. It's still 12 months no matter how you do it.

Nonetheless, there were some very specific folks who said they would use a rolling calendar, and others very specifically use December. This wasn't a question I asked at first, but the information kept being passed on. So I thought I'd better collect this. This must have some importance somewhere.

Five percent don't use a calendar. When I asked them how they kept track of the donations, they said the computer did it, and it never made a mistake.

(Laughter.)

MS. PAPENFUS: Sixty percent said the computer determined eligibility. Twenty percent did manual and 20 percent did the computer and manual.

Interestingly enough, most of the folks that did manual absolutely said -- swore that there was not a mistake. They did not have problems with their donors.

The computer folks readily admit it, that no matter how good their system was, with the exception of a couple, that they knew that some got through, that they missed a few of them. Either things weren't done in time; somebody put the wrong number in. Because they were run by humans there were some problems.

Next slide, please.

As far as what did go wrong, well, donations exceeding 24 a year, 42 percent said, again, it never happened. Fifty-seven percent said, yes, it happened occasionally. Thirty percent had red cells that exceeded the maximum allowable for a year, and most of those were because of both whole blood and apheresis procedures.

Plasma exceeding the allowable per year, about 15 percent, and interesting enough most of those now are coming out of the folks who are doing double and triple platelets because the industry and technology is so much better. We can get that bigger unit and now they're starting to have problems with exceeding the plasma for the year before they meet the 24 times donations for platelets.

And the total volume for all the donation, a small percent said that that had happened on occasion.

As far as what was reportable, they would distribute and report, all eight percent. Ninety-one percent said they would distribute and report none because they didn't feel that there was anything, any law in this case that they were breaking or any issue that was a problem, certainly not for safety of the product.

Plasma pheresis, 38 percent drew infrequent donors, 19 percent infrequent, and 47 percent did none. As far as those that did draw the plasma pheresis, 50 percent said they had none with volume or frequency again. Over the annual volume, 20 percent.

Frequency of donation. What's interesting about the frequency of donation with the ten percent

was that these folks said what happened was they considered them infrequent donors, and they would come back before the four weeks, and they would not have done the medical exam or the protein, whatever else was required, and so, therefore, they were not following through with the criteria, and they didn't want to call them frequent donors. They didn't have a frequent donor system or program, and they wanted it to be infrequent. So those were an issue for them.

It was definitely an interesting survey.

The next one please.

As far as reportable, overdraw volume, there were 11 percent in the group who did plasma pheresis and said they had, in fact, overdraws, especially now, again, with the technology changing and a little bit better.

Too frequent without criteria, about 60 percent would report those. They said that was definitely reportable, and of course, we saw from earlier information from Sharon that it was reportable.

Ninety-five percent would use the product. This was interesting. More than the whole blood. The platelets and plasma they seemed to have no trouble with using it, but the whole blood they did.

So what happened with all of this? And I

know that we're getting -- I'm approaching the lunch hour. So I don't want to be standing in front of you. So I'm going to talk a little quicker, but this is the most important part for me.

Go on please.

This is the questions and answers or -- yeah, I wish. I wish it were the answers -- the questions and concerns from the blood centers and the folks that are out in what -- you know, doing the actual work, the medical staff who's having to make the decisions on a daily basis.

Obviously there was a lot of folks who wanted more data. They were very excited that I was doing the survey, and they wanted to have the results and they wanted to know how many were going to be involved, and I'm going to continue on with this because I think it has been rather interesting.

Very definitely some information, some issues for clarifying the FDA reportable events for both volume, for apheresis, for plasma. There were a lot of misunderstandings about what is truly reportable. One of the questions that came through time and again was always underneath the FDA criteria is what is the product safety. Is the product a quality product? Is it okay?

So if we're doing things that a really aren't affecting the product quality, you know, why is it in error?

And then also, of course, the issues about some of them are reporting things and discarding whole blood, as I said earlier that didn't really need to be. So there are some real misunderstandings out there in that respect.

Some wanted very specific values for overdraw of whole blood. They weren't happy with a plus or minus ten percent or plus ten percent. They wanted to have a number. It was much easier to have a magic number.

Determine if a washed or filtered overdraw unit is a good quality. Can it be used? Again, this was part of the conversation I had with Sharon. She said that she had had several errors reported that they had washed or filtered a unit and then distributed not just an auto but a homologous, and she said she had a hard time with that also because she didn't know what was wrong.

Was that an acceptable unit? And obviously maybe it's a scientific decision to be made as to what's the quality of what's left in that unit.

Next one, please.

Licensing smaller units or not even license them, but drawing them. You know, Ellen talked a little bit about small volumes, not just small volumes to start with. We all know we can draw a low volume unit, but what if you start to draw a regular unit and you don't get the whole volume?

A couple of centers had questions: can I do the same thing that I do with an overdraw? Can I wash and filter or distribute? Is it okay? Is the anticoagulant mix going to be harmful the other direction?

Some real questions about that, and also if they made smaller units, could they draw more frequently because they'd be taking out a smaller volume from a smaller donor?

On the AABB special interest group bulletin board on the Internet was a question posed. Is the 200 mL RBC per week too restrictive? Why not let a spun hematocrit be the determining factor? That was actually echoed many times over in the survey that I did conduct.

I love the last one. Is there a magic number of days? I asked Sharon that one when I talked with her on the errors, and she said, "Magic numbers, we all want magic numbers," and she said, "There is not

a magic number," and she doesn't know it, but if the workshop could come up with one, she'd be thrilled. So it's one of our goals.

Relaxing rates or issues about therapeutic donors, but probably the biggest issue that took the majority of the time at least for my time for the survey was this one about the platelet pheresis. If a platelet pheresis can do 24 platelets a year and at least can do 24 of them in the first six months of the year, what makes them ont an eligible donor the last six months of the year?

That one was echoed time and time again by the centers, and they were asking for the donors. It was interesting. I talked with the quality assurance staff, with the pheresis staff, with medical staff, with donor collection staff, and the pheresis staff, of course, faces this daily because they get the donors who are frustrated when they can't come back. And we all know that pheresis donors are a little bit more committed, I think, than regular donors are.

And they were very angry and they wanted to know why. Why were they okay for six months and not for the last six months?

Some folks got around this by saying they simply did not let their donors donate more than three

times or every three weeks. People did different things with calendars, but the bottom line and the question still remains because the donor could donate in his first six months of the year all 24 times.

You can go on to the next one.

Some of these you can go through on your own. The next one, this one I love. Of course there's always a balance no matter what you do in the world, and this one is don't change the restrictions. There were a couple of them that said leave them alone. They were just fine. The donors are happy, they're happy, and they don't think the donor could tolerate any more pheresis procedures a year.

When I asked them for information, for facts, like what would they use to make that decision, they said that they didn't have any facts except that that's just how they felt. So sometimes we arrive at decisions for different reasons.

A lot of confusion about plasma and platelet apheresis donors and a lot of misunderstanding and a lot of questions about that and suggestions. Make the regulations clearer. They felt that plasma and platelet pheresis overlapped.

Next slide please.

One of the most interesting comments that

came was the volumes of plasma versus volumes of platelets. This one about jumbo plasma.

One of the centers that I spoke with, one of the representatives said that they could draw a jumbo plasma donor on an infrequent plasma program, and that donor could not come back for four weeks, but they could raw the same day a platelet donor and do a triple unit of platelets, and that donor was a platelet pheresis donor, and they could come back conceivably in two days, but the gave the same amount of plasma in the products, and why were those different regulations and where was the safety of the donor involved in that?

I thought it was a very interesting question. I certainly could not answer it.

Granulocyte apheresis, another one. Centers that did that, where does this fit in? How could it be calculated? Obviously they're doing totals on the products that are being collected from donors. Where does this fit in as far as plasma or cells go?

Where do we go now? You know, obviously you need to look at the questions, concerns of the industry. You need to gather more data. You need to look at research studies and what has been going on.

I included on the back of my slides some things that I found interesting and that have been

presented to the AABB this last year about double red cell apheresis, about platelets, large amounts of platelets, about storing blood for a longer period of time.

There was one aspect that I found very interest on extending the storage time to ten weeks.

We need to look at the regulations, proposed revisions of new regulations, and probably most importantly is we need to communicate the requirements very clearly to the industry.

I think that meetings like this are very valuable. I was very delighted to be able to come because it gave a chance to give some feedback from the industry. I think that oftentimes that we don't have enough chance to give feedback or give some information, but probably more importantly is that I want to go back and show this with all of the people that I came from to talk -- the surveys that I took.

There was a lot of confusion, a lot of misunderstanding, and that's a small sampling. So we know that it goes on in a lot of other places.

One of the comments that I want to just quickly make -- next slide please -- is that one of the things about the research that I found very interesting, and this was Dr. Grolin's comment, and

he's our next speaker, in fact, that this was on the AABB special interest group Web site or questions.

The FDA is encouraging people to apply for INDs, to say that it affects the more frequent donations, and that maybe it's a great time to apply for a group IND, and I thought this was a very worthy point to add. I think it's a good place to go from here, to try to figure out some of the answers to these questions.

And in summary, I just want to say that one of the AABB presentations this year that really hit hard for me was an abstract that talked about whole blood and donations, and it was a slide about or a presentation about whole blood questions in 1987 through 1997.

And in 1997, there was an 11.8 percent decrease from 1987 in whole blood donations, but there was a 3.7 percent increase in transfusions, and based on these statistics, they expect a quarter of a million shortfall in the year 2000 for whole blood needs.

So obviously retention of the donors, as well as getting as much blood as possible without hurting them, is very important.

A major concern is obviously safety to the donor and effective product while keeping the donor,

and the data is available to begin to make changes to improve the blood supplies. So now it's just time to put it to work.

And I just want to thank you for your time, and one more slide, yeah. And have a happy holiday.

Thank you.

MS. CALLAGHAN: Okay. We're going to break for lunch.

(Whereupon, at 12:00 noon, the workshop was recessed for lunch, to reconvene at 1:00 p.m., the same day.)

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

(1:03 p.m.)

DR. LAZARUS: Okay. Welcome back.

We are going to continue with Session II. We have two additional speakers. The first speaker I'll call to the podium now is Dr. Jed Grolin, who is representing AABB. He's from the Memorial Blood Centers of Minnesota, and he is going to address the interesting issue of what is a unit.

DR. GROLIN: Thank you for inviting me to participate. I'm mostly representing myself in this talk. Richard Cable was to be the intended speaker a year ago at this workshop, and he was kind enough to share with me a lot of the homework he had done in a number of slides. So Richard Cable is here speaking wearing his member of the 19th edition of AABB Standards hat and is not representing Red Cross.

In fact, what many of our speakers today have already addressed is the fact that many of the things that we're discussing are really fundamental ethical issues, our duties to the donor, our duties to the recipient.

And so today I want to start off with a bit of a digression and do ethical issues of blood transfusion, talk about the physical effects of volume

depletion, but then get back to the ethics. So not only how much can you take, but how much should you take.

I want to distinguish volume out in the typical whole blood collections setting from isovolemic hemodilution, i.e., the zippy stuff that these new automated machines can do.

And finally, to address recipient concerns.

There's a wonderful review by Steve Kleinman and Rel Shapiro in the audience here this morning on ethical issues for blood transfusion. This entire area is imbued with issues of ethics. Our donors don't get anything. They're doing this out of the goodness of their heart, and hence we owe them a responsibility to treat them in an ethical fashion, and ethics actually has a science to it and could be divided into various principles of which I will wax poetic on only a few.

Those include "primam non nocere," above all, do no harm; justice, treating people fairly. Truth telling is fairly self-explanatory, but autonomy means allowing people to decide for themselves.

We should also be providing a benefit, respecting the person, and keeping promises, both explicit and implicit, such as proper use of the gift

of the unit.

As health care providers, it is our responsibility to protect donors from harm. In fact, I will show you a lot of donor fainting data, as well my colleague Rebecca Haley. Somehow that's okay, and in fact, there really is no weight or volume that one can do without some of the donors fainting. I may do that in front of this audience myself.

However, when one considers in the typical hospital or medical care setting about a procedure, one is balancing its risks versus its benefits, and the current data regarding a little iron depletion being good for you from a cardiac standpoint notwithstanding, there really is no clear medical benefit. People are not, we hope, donating blood because of some medical benefit. They're donating it because it's the right ethical thing to do.

Well, if there is no clear benefit, then there really ought not to be any clear significant risks.

Justice means treating people fairly and equally, and while I do want to emphasize that donation is a privilege and not a right, it is still problematic to be discriminating against individual groups, as Dr. Lazarus has commented, and in all due respect to Dr.

Lazarus' size, this includes petit females as well.

Finally, we need to be talking about fairness from the recipient standpoint. When a doctor orders a unit, what is it that the recipient ought to expect? Is there a minimum amount of stuff that is okay?

Truth telling and autonomy are often tied back to consent. We should be telling donors and recipients the truth about risks, and we should be allowing them to decide and have similar issues apply to both recipients as well as donors.

So where are we now? Well, the 19th edition of Standards made something of a departure from prior editions in introducing the limit of 10.5 mLs per kilo, and hence when the average collection person heard about that, we're going, "What were you thinking? Do we need a scale at every collection site?"

And I will come to the answer. The answer is no. However, it does not make much physiologic sense that one should be as concerned about drawing a certain blood volume from me as Dr. Lazarus.

Where did the 18th edition in previous limits come from? It came from the limit of 525 mLs now that was generally applied to the 50 kilo minimum donor, but it was really rather an arbitrary cutoff.

There was a real ethical problem with that standard. While Linda Papenfus has provided us with an interesting survey, although a majority of donor centers may be using the 450 mL bag, a majority of donors are getting donated into a 500 mL bag. It is simply a fact that the largest blood collection agencies are using the 500 mL bag, and therefore, a majority of collection agencies were not doing something according to the standards, which ought to suggest that maybe there was something wrong with the standard.

At the same time, the Red Cross was doing their wonderful study that Dr. Haley will talk more about that looked, in particular, at sinkable rates among the smaller donors.

Well, this gets us to the issue of sinkable rates, but before one addresses that, one has to address issues of blood volume, and in fact, blood volume is, in fact, a function of height, weight, and gender, and to overly simplify many elegant and complex studies for the same height and weight men have higher blood volumes, to wit, talking about a 110, five pound donors, if that donor is female, they have an estimated blood volume of around 3.1 liters. If they're male it's closer to 3.5 liters.

If you were talking about the maximal draw into a 450 mL bag, that's around 525 mLs if you include the now 25 mLs of samples in this advent of NAT testing that takes an additional seven mL sample. So you're talking about taking out as much as 17 percent of the donor's blood volume.

Bring that to a 500 mL bag and you're now talking approaching 18 percent, whereas for man it's closer to 15 or 16 percent of that same weight and weight.

Well, syncope or vaso-vagal attack can be provoked in all subjects by withdrawing a sufficient quantity of blood, and Dr. Wintraub in a wonderful history of hematology book, A Blood, Pure and Eloquent, describes the era prior to their blood being collected in bags, a good anticoagulation and storage. They would have Harvard medical students standing up in the surgery room giving direct vein to vein transfusions.

Well, as you can imagine when you're giving a direct vein to vein transfusion, it's very difficult to ascertain just how much blood has gone out of the donor and into the recipient, and they knew when to stop by when the medical student fainted, which makes me glad I went to Yale.

(Laughter.)

DR. GROLIN: If one defines syncope as really any icky symptom, any sign or symptom of pallor, sweating dizziness or nausea, one 1940s study found five to six percent of donors included. If one is more strict, i.e., mere or full loss of consciousness, that's actually somewhat less than three percent.

Syncope rate is a function of the amount of blood drawn, donor size, and experience, and gender actually, as Dr. Haley will tell us about. Syncope is more common among first time donors, about five percent of first time females, about four percent of first time males in a Tomasulo study from 1980, but only about two and one percent respectively in repeat donors of those same genders.

Well, back in World War II, and there's a wonderful new book on blood. I'm thinking Douglas Adams, but that's not right, which really talks about the origin of blood collection during World War II. World War II really stimulated a lot of blood banking prowess, including there were people dying of lack of blood, and so people were quite willing to push the envelope on just how much blood can you get from a donor.

And so a study out of England in '42 observed a definite relationship between amount donated

and syncopes. You went from around four percent to nine percent, increasing from the 400 to the high 500 range. You could increase that to about 50 percent if you went up to almost a liter and over 50 percent if you exceeded a liter.

Since many of the donors were male servicemen, this is not quite as scary as it looks.

You could get that to almost 100 percent by getting to a liter in under 15 minutes, and if you really pushed the envelope to one and a half liters, you could get virtually every donor to keel over.

(Laughter.)

DR. GROLIN: And they bounce back up. It's okay.

Well, the 19th edition of Standards was confronted with the issue that, in fact, a majority of blood centers were already having a variance to use 500 mL bags, and so we addressed the question: should we be concerned about safety, especially at the lower end?

Well, in fact, there was already some very reassuring data collected by New York Blood Center, and we thank Celso Bianco for this. This is part of the submission of New York Blood Center to the FDA for their variance or the AABB for their variance, and it showed that when they went from the 450 mL bag to the

500 mL bag, there was really no statistically different rate overall in reactions, mild, moderate, severe, or you might say, "Well, gosh, you're taking more blood. You're going to make everybody anemic," and there was, in fact, no increase in either hemoglobin deferrals or incomplete.

So looking at the blood center overall, there really was no adverse effect of going to the larger bag size.

Dr. Haley will give this study in more detail, but suffice it to say that ARC did a very nice study looking really at very specifically sinkable rates and the contributing variables, including the fact that female, young, first time, low weight and low pre-donation blood pictures had higher absolute reaction rates, but when one actually analyzes for independent variables -- which of these variables independently predict on only age, weight, and donation status? -- and so age under 20 and weight under 120 pounds were particularly associated with donor syncope.

Actually the single biggest thing associated with donor syncope was first time donation status, and so one wonders if the Red Cross is going to have people start with their second donation.

PARTICIPANT: We've (inaudible) that.

DR. GROLIN: That's a joke. It's after lunch, and I'm trying to --

(Laughter.)

DR. GROLIN: Unfortunately this was an exceptionally poor choice of colors, but I don't want to let you -- and I think you'll see much better by Dr. Haley's slides. Although the sinkable rate is higher among donors between 110 and 120 pounds than it is among donors that weigh more, that difference is really rather incremental.

So it's four per 1,000 for the 120 to 129 group, and it's 4.6 per thousand for the 110 to 119 group. So it's higher, but it's incrementally higher.

Put that more quantitatively, reduction of weight by about eight percent from 120 to the 110 pound group leads to a 15 percent increase in sinkable reaction. Fifteen percent increase sounds like a lot, but again, you know, that's four to 4.6 per 1,000. That's what we're talking about.

Similar results would be expected from an 11 percent increase in volume, although the New York Blood Center data collection was not done by donor weight. So we can't actually have that independent data.

So what did we do with this data? Well,

the 19th edition of Standards thought it didn't make a whole lot of sense to say, no, you cannot -- you know, 525 or 550 mLs is okay for a petit female and someone of my I guess now girth, and we said it makes more physiologic sense, especially now that we're being forced to draw more and more, especially with an increase in NAT samples, to make a size specific limitation.

And while there are far better estimates of blood volume than just 10.5 mLs per kilo intending to be 15 percent of someone's blood volume, any limit you make is going to be arbitrary, an arbitrary cutoff on what has occurred, and hence we simply set it at 10.5 mLs per kilo because that was the traditional 525 mLs per kilo.

What we were functionally saying is, "Fine. Go to the 500 mL bag, but if your donor is between 110 and 120 pounds, no. Aim low. Don't get up to the maximum amount in the 500 mL bag or you're going to have higher fainting rates."

In fact, in practice, since bag sizes are still limited, even though I am Gargantuan, you're not going to be taking two units of blood out of me. You'll still be taking one unit of blood. So bag size, in fact, still creates a practical limit on whole blood

donation volume.

Well, is more better? Well, during World War II when people were bleeding to death for lack of supplies, all of those what we cringe at studies actually made a whole lot of sense.

However, we're not really having people dying in the streets, although the national blood collection data is somewhat concerning. It should not be lost upon you that in Japan the standard size, or so I am told, is half a unit or what we call half a unit. I guess they call ours a double unit.

At the same time, we've also heard with both concerns about the adequacy of the nation's blood supply as well as issues of donor exposure that, in fact, I think we still have an obligation to obtain the maximum gift up to the points of donor safety.

Okay. So we've talked about what can we take out of a donor. What should be in the unit? Well, the packed cell volume varies greatly depending upon both the volume drawn and the hematocrit of the donor.

Why are we giving red cells? We're giving red cells so that they can carry oxygen, and the stuff that carries oxygen is hemoglobin. So really what should define a unit is how much stuff there is in it

that is achieving the therapeutic effect.

Now, this does vary tremendously, to wit, if you have a weeniest (phonetic) possible unit, 405 mLs, and the lowest allowable hematocrit, that would yield a packed cell volume of only 154 mLs. If you have the mondo unit with a crit. that would border on evaluating the donor for polycythemia, you could have really almost twice the packed cell volume. Both of those are perfectly allowable, but those come from variables that are really not under regulatory control. They're under -- well, you know how the bumper sticker says "Stuff Happens." You know, donors happen. They happen to come in in various sizes.

So a unit should be defined by its therapeutic equivalent of the stuff we're intending to transfuse, hemoglobin.

Now, a 450 mL draw from a donor with hemoglobin of minimum allowable hemoglobin concentration, 12.5, contains 56 grams, and if you were to go down to the minimum size unit, 405 mLs, the absolute minimum would be 50 grams.

And so Dr. Cable and I as individuals are proposing that if one wants to have a content minimum, that 50 grams of hemoglobin -- it's a round number -- would be a wonderful suggestion because as our current

standards, I mean, we are going quite consistent with what is standardly happening, and so what people should be led to expect is if it's less than 50 grams of hemoglobin, it probably should be labeled as a weeny or low volume or low hemoglobin unit.

I wonder if "weeny" is going to get its own 128 label.

(Laughter.)

DR. GROLIN: Interestingly, the hemoglobin limitation of 12.5 grams applies to both men and women. The origin of this is somewhat obscure, and what's interesting about it is 12.5 grams is actually quite a bit above the normal lower limit for females.

While one might talk about this as related to patient efficacy -- well, you don't want to give the recipient too little -- I mean, if you're drawing a 550 mL unit from somebody who's got a hematocrit of 38, that's still say over our 50 grams hemoglobin minimum that ought to be in a unit.

And so if one looks at studies of people who are shown not to be iron deficient, people who are demonstrated not to have iron deficiency, the normal range for females goes down well into the 11s.

This is not just an academic statement. Another branch of government has already defined what

is anemic for you. The CDC has cutoff criterion for anemic, and also, again, they have defined 36 as the cutoff for females in being anemic.

Well, in a way it should not be lost upon you that part of the reason for this workshop is that the advent of zippy new devices, the apheresis collection devices, has really forced the agency to confront, well, now that we're collecting devices where you can make any size units you want, it is perfectly appropriate to be saying, "Hey, let's not have somebody collecting 800 mLs of plasma and, you know, sending them out in 100 mL units and saying, hey, this collects eight units." That does not seem consistent with what we're doing.

Furthermore, we have minimum concentrations for what's a platelet apheresis unit, i.e., three times ten to the eleventh. So why not for red cells and plasma?

In fact, functionally by establishing minimum hematocrit for donors and having six bag sizes, we have effectively established the 50 gram hemoglobin, 150 mL packed cell volume as the minimum red cell content, though I will address plasma in a minute.

Can you hit the focus again?

Well, this now needs to relate the

distinction between isovolemic hemodilution and volume out. The thing that makes people faint is not the loss of hemoglobin. The thing that makes people faint is loss of blood volume, and people are far more tolerant to isovolemic hemodilution, i.e., taking stuff out but putting other stuff, saline, back, or even the slower removal that the automated apheresis devices entail.

So what are these pheresis devices? Erythrocytapheresis is the removal of red cells, erythrocytes, by an automated device that withdraws whole blood, spins it, separates the red stuff from the clear stuff, which is the opposite direction of Larry's slides, and returns the plasma, and when significant volumes are being taken out, also saline or some of the replacement fluid, as the whole blood is removed.

The limit to hemodilution is really a function of being able to meet tissue oxygen requirements, not fainting, and we've learned actually a tremendous amount from Jehovah's Witness studies, and to overly simplify them, many studies, several by Dr. Carson out of New Jersey, can be sort of summarized into the following:

That not a whole lot of people get in trouble above a hemoglobin of six, which is about a hematocrit of 18;

That mortality below a hemoglobin of six is often related to preexisting cardiac disease;

And that when you get below a hematocrit of ten, that there was, in fact, significant mortality.

In large part, people's ability to tolerate extremes of hemodilution is their ability to have cardiac compensation, to wit, if I'm sitting at rest, I probably have a cardiac output of about five liters a minute. If I was running up several flights of stairs or perhaps my speaking to you right now, I might have a cardiac output of 25 liters a minute, about a fivefold increase.

Hence, it should not surprise you that if my only job is to lay there on an operating table, that I will tolerate a fivefold drop in my hematocrit from 45 down to nine or ten because my heart can just increase its output.

Our donors, however, are not Jehovah's Witness patients. Well, it is possible to hemodilute somebody down in hematocrit and not kill them. It doesn't mean it's the right thing to do. They're not expected to go to work that afternoon.

In fact, on the other extreme though, it's reasonably well shown that in hemodilution down to about a hematocrit of 30, unless you're really doing

true aerobic exercise and know your climb in a mile, et cetera, you're not likely to notice a hematocrit down to about a level of 30 in your normal day-to-day exercise. At least while I sit in front and answer 40 E-mails a day is not exactly aerobic stress.

Recognizing that, we were nonetheless concerned on the 19th edition of AABB Standards that there was no standard on how low you could go, and so admittedly arbitrarily, we said we don't think makers of these devices should be intending to drop people's hemoglobins and hematocrits less than ten in 30, and in fact, the already approved FDA algorithm for one of the devices was, in fact, consistent with that, but it was, in fact, dropping people's hemoglobins to ten, and there was actually donor safety data that the donors were pretty happy as a clam, and if anything, had less reactions because they weren't having the large, acute volumes out.

There's also no standard as to what the packed cell volume content should be in apheresis units. However, Standard H2.130 does defer to FDA requirements. So we were throwing the ball to the FDA, and I guess now the FDA is throwing the ball back to us, which is only appropriate.

In fact, most licensed devices provide a

packed cell volume of 180 to 200 mLs consistent with the volumes that we're currently obtaining. So I think the manufacturers today have been very responsible in providing really the same sort of size units as one expecting the median at this point.

Furthermore, we extended the same 10.5 mLs per kilo out of body experience to apheresis devices because in order to prevent -- thank you, Berella (phonetic), for catching the joke there -- to prevent excessive sinkable events because there are, in fact, some discontinuous apheresis devices, and one would not want to expose a donor to any greater risk in an apheresis device than a whole blood.

Well, why would anyone in their right mind use one of these apheresis devices? In fact, we have an ethical responsibility -- you can see we don't buy them any Gucci bags in my household -- we have an ethical responsibility to make the best use of the donor's gift, and in truth, guess what. We do outdate like everyone else here AB red cells.

And so it is consistent with our fiduciary duty to donor and recipient alike when the O negative donor comes in to get extra red cells from them or the AB donor comes in, to get extra plasma from them because that, in fact, makes the best use of their

gift.

Well, this also addresses the issue of how often apheresis. Little did the FDA realize that I was a spokesman for them, huh? That was actually done after a long conversation with Dr. Lee. So I didn't make that all up.

Whole blood donations defer the donor for eight weeks, and the FDA logically said, "What's two times eight? Well, that's 16, and let's defer people for 16 weeks."

In fact, if one is talking about time to repletion of red cell mass, there is reasonably good data that is older than I am, but not by much, that donor's red cell mass is replaced in about three to four weeks from a whole blood donation.

Hence, it shouldn't surprise you that in a Dean Elfath study of two unit red cell donations by apheresis that it took about twice that time, about six weeks to recover red cells.

Now, I will admit there was another abstract at the 1999 AABB meeting which did show that if you are repeatedly taking two unit donations, that iron deficiency can result. It was not -- actually interestingly, Cheryl Schlichter (phonetic) did a study using frequent whole blood donors and frequent

apheresis donors, and guess what. They had an identical rate of acquired iron deficiency. It doesn't matter so long as you're taking out the red cell mass. You're going to get about the same amount of net iron out.

Now, that is treatable by steak dinners, but my wife increasingly feeds me tofu, which actually I like.

Well, also from a patient perspective we need to recognize that units -- while as pediatricians have always been savvy enough to order by cc's per kilo, most of the rest of the world does not view the patient from the same variable size perspective that us pediatricians do and tend to order things by units.

And what should the doctor and patient expect from a unit? And how important is that consistency? Is there any outcome difference if the person's hematocrit goes up by three percent or five percent? Probably not a lot.

It does get worse than that, however. Remember we're talking about the units may be variable in size, but if you're taking those variable size units and transfusing them into us variable size people, you're going to magnify the effect of that discrepancy, to wit, the 405 mL hematocrit of 38 percent weeny unit

of packed cell volume, 154, about 50 grams, that will only increase, if you put that into me, will only increase your hematocrit about two percent, while if you take the maximum hematocrit in volume unit and put it into a smaller female, that may increase the hematocrit nine percent.

So you can have a fourfold discrepancy in outcome simply by the variables that are in the system.

I have talked about minimizing donor exposure, and I do have some ambivalencies. On one hand, the current risks are incredibly low, and being one of the 16 NAT labs in the nation, I'm excited to think that they may be even lower in our near future, to wit, the current risk of HIV is published at one in 676,000, and one would expect after NAT testing that Hepatitis C risk will become similarly low, but they're not zero, and they never will be zero.

Hence, having the number of donor exposures by definition reduces the transfusion transmitted disease risk by half, and hence I think reduction of donor exposure is still a worthwhile goal.

If one were to give the same two red cells to a patient, I suppose that the apheresis devices could be superior in that respect, but in fact, the most practical standpoints those two units are being

transfused independently.

But there are also other novel components, and if I want to put one point into your mind, however perplexing the idea of what should be in a unit is for red cells, at least the bag sizes historically fix that. The volume that should make up a plasma unit is even more confusing, to wit, we collect some jumbo plasmas at 600. How many units are there in 600 mLs of plasma? As my Yiddish grandmother might have said, "Ver vast?" Who knows?

Yet plasma is marketed and billed for by the unit. We charge the same price regardless of how weeny or how fat it is. Yet package sizes vary considerably, which is a function of bag size, component preparation, and donor hematocrit.

So if one takes a minimum volume unit from a maximum hematocrit guy like me and then goes and makes a platelet out of it, you've just stolen an extra 50 to 75 cc's of plasma out that. So theoretically you could get as small as 150 mLs.

In practice, I actually for this talk had us pull a bunch of units and did some physics on it. Our median is 250 mLs. When we were going the 450 mL bags you might expect that it was a little closer to 225, but our range was 200 to 344. So there really is

a tremendous range.

While this variability is problematic, it is true that the other folks have an alternative to solvent detergent (phonetic) plasma which is consistently 200, but it's not lost upon me that it's consistently smaller.

So what's better? I don't know, which gets me back to the summation. I think we have to think of these questions in terms of what are our ethical obligations both to donor and recipient. We must maximize donor safety, maximize the utility of the gift, consider recipient safety, including minimizing donors, and recipient justice, no shortchanging the patient.

And so we have actually rather concrete proposals for the FDA, and these include the suggestions that the FDA adopt AABB Standard B-1200, which is the 10.5 mLs per kilo out of a donor at any one time. This is unreplaced volume.

That they adopt the Standard H2.131, which is that the post donation hemoglobin hematocrit should be at least -- be equal to or exceed ten grams in 30 percent hematocrit. That doesn't mean that after every double unit apheresis donation you would need to check each and every single donor, but in your validation you

certainly should.

And that they define a red cell unit as a minimum of 50 grams of hemoglobin.

Now, this actually has a very interesting corollary, and that interesting corollary is that this would allow donations from donors down to a hematocrit of 36, and that's because if you take a whole blood unit from a donor whose hematocrit is 36, you cannot get them lower than a hematocrit of 36 -- I mean 30. So the safety studies have already been done from the double red cell unit studies.

If I for some strange reason would have -- let's say a large female because that would be a little more physiologically believable. My mother is five, ten.

If my mother came in to donate, who is a big woman and has a hematocrit of 36, you are not going to dangerously deplete her blood volume by allowing her to donate.

Furthermore, her hematocrit will not go below 30 which is already proven to be safe.

So we would suggest allowing donations from hemoglobins down to 12 and down to 36, consistent with that physiologic data I presented.

And certainly at the very least apheresis

donors, the current limitation of 12.5 or hematocrit of 38 makes absolutely no sense since the chance of losing your red cells is minimal. Even if you do, you never lose more than 200 mLs packed cell volume.

So I will end there before I get chased off the stage.

DR. LAZARUS: Thank you, Dr. Grolin.

And the last speaker in this session is Dr. Rebecca Haley. She is the senior medical officer with American Red Cross Biomedical Services, and she'll be presenting additional data on volume of product collected with respect to donor blood volumes.

DR. HALEY: Thank you, Dr. Lazarus.

There are advantages and disadvantages with being the last speaker in a section. One of the disadvantages is most of the other people have already covered most of my slides. So we can go pretty quickly.

Dr. Lazarus has covered the regulations, and Dr. Grolin and I were in the same Standards sessions that set up the AABB minimums and the donor protections, and so we've been a part of a lot of the same discussions.

But here we go. We will go through my math exercises. The people at the Red Cross know that I'm

very fond of bringing my calculator to these sessions where we talk about these things and say, "Okay. Let's see what you really can do, what you really should do."

Oh, I see. We have a small guy.

So the donor volunteers to help a patient, and just as Dr. Grolin said, what protections are in place for the donor? Because we at donor centers have a duty to that donor to protect them, but then we can't send things to the hospital that are substandard either because the blood component volumes are large or small for transfusion services. How do they handle it? Do they have differences in the way that they transfuse or plan to transfuse a large and a small unit?

And if a whole blood donation was 450 mLs, as it was in the CFR and till the last allowed for the 500 mL bags, and the plasma donation allowable, according to the FDA memorandum of November the 4th with the simplified nomogram that was proposed by Dr. Forrest, the algorithm permitted plasma collection per body weight, and the apheresis machines with on board computers use a more complex formula, but which is actually a little more conservative than the one that we came up with in the AABB standards committee, such as the Nadler and Allen formula.

And I sat down. As I say, I like to play

with a calculator when we get into these things and figure out how that does compare with the 70 mLs per kilogram that we used in our AABB deliberations, and we found -- and then I picked up, and I said I'd be entirely fair. I picked up my Solkirk (phonetic) Physiology from years ago and said, "What do they say about blood volume?"

"Blood volume can be measured by injecting dye." I said, "Well, I don't think so, not in healthy donors." But, they said, if you have a 70 kilogram man, he will have about a five liter blood volume. Well, you figure out 70 mLs per kilogram, and you'll get 4,900. So that was pretty close.

And they said that the woman's blood volume would be about 500 less than that, and another interesting thing happened when we put out the standards, the 18th edition, which was the first time that we mentioned the 15 percent blood volume limit.

I immediately got a call from one of the Red Cross physicians, and he said, "Just look in Guyton. You know that the blood volume is 85 mLs per kilogram."

I said, "Do you know who Guyton was doing his blood volume experiments on? It was athletic, male medical students."

So that's where you have your range, probably from 85 to 85 mLs per kilogram.

What we tried to do was to pick some kind of an average that would be fairly conservative, that would allow the donors -- allow most donors to be collected without having a complex algorithm that we didn't think people could handle.

In fact, infants have about 100 milliliters per kilogram, and then as you grow older and less of your body mass is muscle and organs, then your milliliters per kilogram go down.

Well, oh, there. Maybe I can get it.

This is supposed to represent Dr. Grolin's governor in his body shape, and we don't think --

(Laughter.)

DR. HALEY: -- that the blood volume is proportional all the way up because probably limiting out at about 80 kilograms the blood volume doesn't grow nearly as fast as the size, unless you happen to be a very well conditioned football player, and not a very high percentage of our donors are.

So now calculated limits on donation, and around here a little bit. And so here we start with some of the math that you're already heard. A 50 kilogram donor with 70 mLs per kilogram has a 3,500

milliliter total blood volume. That's where you figure the 525 mLs total collection, and with a standard whole blood bag with 500 mLs collected, test tube and tubing -- in our system we weighed the tubing, too -- was 38 mLs, and so you had a total then of, yeah, 538 mLs when the limit you're supposed to collect in this person was 525.

So you're pushing the top, and I know that we have on file a variance from Katheryn Zoon saying that it was okay to collect 500 mL bags from a donor over 110 pounds with a ten percent variance on either side. So, you know, these edges get a little fuzzy.

Well, how much of the red cell taken if a person has a hematocrit of 38 percent? Then if you had a blood volume of 3,500, your red cell mass was 1,330, you donated 200 mLs of blood, you went down to 3,130 and you redivided, your hematocrit is now 32. That is a little bit in excess of with Dr. Grolin was speaking about when he was saying maintaining the 30 percent hematocrit post donation.

Okay. Let's flip over to plasma for a moment. The FDA memorandum actually allows an 18 percent blood volume in the donor if you subtract the 20 percent citrate that they expect to find in the plasma, but again, that is isovolemic hemodilution, and

I don't think that bothers folks because they're getting their volume back as they're giving their plasma out with saline and so forth.

And you don't push the 15 percent limit as you go up. Okay. The effects, again, that we would expect if we over collect would be volume depletion from any type of donation, anemia, depletion of iron stores or depletion of protein stores.

Now, in the Red Cross, we don't do frequent plasma donations. So that's usually not a problem, but what about the 70 kilogram person? We'll just go through one more math problem. I promise that's the end.

With an estimated blood volume of 4,900 mLs, and let's say they have a 40 percent hematocrit, which is pretty normal. Now, to equate the 50 kilogram, 38 percent hematocrit donor's gift, the 70 kilogram blood donor -- I did the math twice -- can give 390 milliliters of red cells and still have a hematocrit of 32, and that, of course, is the double red cell rationale.

So then let's talk about the size of the unit, and honestly we did not get together on this until this morning, and we seemed to come out pretty close.

A normal kind of unit of 490 mLs, if you drop that hematocrit down to 38 percent with 450 mLs, you have 180 mLs. If you have a 500 milliliter unit with 200 milliliters of red cells, then you have 200 milliliters.

And so as it turns out, with apheresis machines the red cell volume can be set in a wide range. I was surprised how widely the range could be set when we started setting up our protocols for collection.

We decided that to have -- to distribute a red cell unit that was less than the minimum hematocrit unit of the standard size bag that we were distributing was not very fair, and so if we had a choice of where to set the standard unit, we should do it at least at the minimum size of the standard unit that we should be collecting.

And so there's one thing that has been woefully lacking in this conference so far, and that is very complex graphs that are very difficult to follow, and so I'm going to fill that deficiency right now.

(Laughter.)

DR. HALEY: We did a study, and this is addressing the problem of donor reactions. We did a study of 70,000 donors, and different from the study

that Dr. Grolin was quoting that was done in the northeastern section of the United States by the Red Cross where they looked at people who reacted. We looked at people. We looked at the donors, period, and constructed a database of these donors, and I did this with Dr. Foulsey Wyhob (phonetic), who is a statistician at the Red Cross.

We went through all geographic sections in the United States. We did small, medium, and large centers. We made sure that we included high school blood drives, community blood drivers, and plant blood drives so that we had pretty much -- and we did all seasons of the year.

Who can tell me what season of the year has the most blood donor reactions? Second guess? No, it's the spring, and it's the spring, and we think it's because that's when we really hit the high schools hard, and the high schoolers have higher blood donation reaction percentages.

The other thing that we captured, gender, age, weight, blood pressure, pulse, and first time versus repeat donor status. We captured a lot more than that, but that's all we'll talk about today, and what we found that was a younger age, first time donation, a younger age was important. That was

statistically significant.

First time donation, any age, you're twice as likely to have a reaction, and females are always more likely than males, and there's a weak association with lower weight, but it's not very good. It's not very strong, not as strong as the other two.

And what we also found with this model, and I didn't bring my computer with me, but you can put in your gender, your weight, and your first time or repeat donor status, and we can tell you what your reaction percentage chance is going to be.

So we did it the other way so that it could be predictive.

But this is what we constructed it from. I'll turn it around here so we can see.

Now, by age you can see that the girls, if I can make this work, have almost ten percent reaction rate at 17. So they are the very highest. First time donors.

Now, if this is the second time, they are pretty good. They're down to about four percent. These are mild, moderate, and severe reactions. These are not -- the other thing about the Trouern-Trend, Cable and group study is that I think they were moderate and severe reactions. These are mild,

moderate, and severe, as marked on the donor record.

And the other thing is that the guys are a little less, but you know, here are the first time donor guys. They're not too far down, but the repeat donor guys are here.

In this 70,000 donors, the average weight of the guys was 40 pounds more than the girls. So that was different from what we heard from the plasma sector.

Okay. Now, let's see. The one we did before was by age. So you see as you get older you're less likely to have a reaction.

Now, what about weight and weight strictly. If you take 110 pound people, if it's a woman -- no, these are all boys; these are all guys -- and the first time you give, if you're 17 -- no, the first time you give if you're 110 pounds. I'm sorry. We took age out of this one. You have a six percent chance of having a reaction. A 110 pound man who is 41 -- I'm sorry that's hanging off the slide there -- has only a little over a two percent rate of reaction, and if you are 71, your chance of reacting is about .5 percent.

So we're really surprised. If you get to older folks, they don't react very much anymore. I don't know if their autonomic nervous system has had to

handle everything and it's tired or I don't know.

Okay. Here are our girls. Almost nine percent at 110 pounds, but there's no sharp drop-off when we hit this magic less than 15 percent blood volume drawn. It's a very gradual slope downward, and then it corrects almost completely.

And, by the way, the average reaction for blood donation in this big study was about three percent if you averaged all these guys together.

And another thing that we do not capture here that's very interesting is the girls. This is the percentage of people reacting. If you looked at the total number of donors, we do a great job of getting donors here in the high school years, if we were pretending this was age. We have a bunch of them that react, and then it drops down to about half of that for years before it starts going back up again.

So by allowing the people to come in and react, they may self-select and not come back. So it may be that some people are more prone to reaction than others and they just don't come back, or maybe the second time it's not as scary. I'm not sure.

Okay. So here's a composite of the last three or four slides of men and women by weight, again with the girls on top and the boys really not far

behind, and we know the boys tend to be -- but these are at the same weight. So at the same weight even the genders are not that different. And by the second time you do it, you do much better.

So what do we find from our donor weight reaction studies? That age and first time donor status are important predictors, and that weight is a weaker independent predictor, and that all donors collected in this study remember were within current weight limits.

So we didn't test the limits. Actually the reason we started to do this study in the first place was the Red Cross had an upper limit for donations of a pulse of 110, and we'd had that since forever, and the AABB -- I mean it was first recorded in 1974. So from '74 to '98 we had the upper limit of 110.

Well, that was not according to AABB standards, and we said, "Well, give us a variance, and let us study it, and let us see if it makes a difference."

And sure enough, right at a pulse of 100, between 100 and 110, we had a very sharp upturn of the number of reactions. So the physiology books are right. A hundred is about the highest normal pulse.

So that was why we did it in the first place, but we got this other information which I think

is fairly relevant here, and in summary, the current rules of blood donation do a good job of protecting the donor from reaction, and staying within these rules, the time and effort at each blood donation can be better assigned.

That means that if the larger donor can give more components with the new pheresis devices, if you very carefully follow the algorithms that protect their blood volume and red cell loss so that they are at acceptable minimums when you get through, then I think that we've done both the patient and the donor a service.

And that donor protection protocols must be observed. We really believe that strongly.

Thank you very much.

DR. LAZARUS: So at this time I'd like to invite the speakers for Session II to come sit on the panel.

MS. CALLAGHAN: Okay. If anybody has any questions of the speakers, come up front.

DR. HOLLAND: Paul Holland from the Sacramento Blood Center.

I wonder in lieu of what Linda Papenfus said if someone from the FDA could comment on the record for us on the use of blood and blood components

and reporting re. errors and accidents of components drawn inadvertently earlier than the collection date from donors that are otherwise qualified, because there does seem to be a lot of confusion out there about the use of these and whether or not these are errors and accidents and must be reported.

MS. CALLAGHAN: Unfortunately I don't think Sharon O'Callaghan is here because she would be the one to have that data, but if you will submit that question I'll have her answer you. I don't know the answers to that because I don't have access to her database. Sorry.

DR. GROLIN: The other thing I wanted to stress to the group at large is we would like to use Standard Source as a medium by which to communicate and put in writing answers to useful questions that you get. So when you are making an answer to Paul, we would like to then share that in Standard Source as an answer to frequently asked questions.

DR. HEATON: I'm Andrew Heaton of Blood Systems.

We've heard a lot of discussion today about what a unit should look like and what you think a doctor's red cell mass is, and I've been involved in doing a number of studies to look at that in a very

precise way, and one of the issues which drops out is that in today's environment, with people's current dietary habits, the red cell mass is much smaller than the nomograms would predict.

Indeed, in a large study which if we have time I will show you, the average red cell volume is about 20 mLs per kilogram in males and about 26 mLs per kilogram in females.

Now, if we go with the larger red cell volume or we reduce the hematocrit requirement, I'm concerned that you are going to remove greater than 25 percent of the donor's circulating red cell mass.

In addition, we've also done paired studies on donors and looked at their capacities to regenerate their red cell mass, and we observe that women of 130 pounds or less on the second occasion when you perform their red cell volume, it was more than five percent less than on the first occasion.

That is to say that those individuals were unable to rebuild their red cell mass during the 56 day period.

So I think the comment I would make, and if we have time I will show you the data, is that we need to be very careful about pushing the envelope with red cell collection because unlike plasma where the

proteins have a short half life, red cell synthesis is very strictly limited, and in many cases people's dietary intake simply isn't good enough to support significant red cell synthesis.

So I would urge that standards that focus on red cell donation, particularly two unit red cell donation, very carefully examine the donor's real measured red cell volume, not the Nadler one, not the Hurley or the DuBois one, but the real measured red cell volume to document that you are, in fact, not rendering your donor anemic by collecting units at low hematocrits or collecting very large units from people who cannot resynthesize their red cell mass.

DR. HALEY: Dr. Heaton, do you suggest that we do red cell masses on our donors before taking a double red cell, or do you think the hematocrit serves?

DR. HEATON: The relationship between hematocrit and total red cell mass isn't that great, but if you add to it -- particularly in smokers -- but if you add to it weight and age and sex criteria, you can come much closer than we now do.

And so my suggestion would be that we encourage the development of an algorithm that would pick up those variables if we wished to deviate from a standard, from a simple standard.

So we might wish to maintain a simple standard, but then have some additional criteria under which organizations could deviate that would include sex, that would include weight, or would include hematocrit.

DR. KLEINMAN: Steve Kleinman from UBC.

I have two questions that were raised in the introductory remarks that I don't think any of the panelists actually dealt with, and the first one is what are the recommendations for the weight limit. Is there anybody who thinks we can go down below 110 pounds and safely draw donors?

DR. HALEY: I don't suggest it. In our organization we decided not to, particularly in light of having 500 mL bags as our usual bag. Five hundred is pushing the top, and you can't go all the way to the top in the 500 mL bag.

DR. GROLIN: I guess as a pediatrician who had a large autologous program, we actually had a very large experience in growing lots of donors that were below 110 pounds. There was an overriding reason to do so. These were autologous units for pediatric patients.

So there's absolutely nothing about the 110 pound. I mean we had donor reaction rates that were no

higher than those that you've seen today. So there's absolutely nothing magic about the 110 pounds.

In practice, like Becky, we in Standard Source under B-1200 do a table showing the volumes, the maximum volumes you can draw using the 10.5 mLs per kilo, and if you have someone who is below 120 pounds and you're using the 500 mL bags, you already need to do something special.

So we've had to add on our uniform donor history the question do you weigh at least 120 pounds to insure that we're not exceeding that limit.

So if you were to try to draw someone who was less than 110 pounds, you functionally cannot use the 500 mL bag. And then when you extend it to what Dr. Cable and I are suggesting, a minimum of 50 grams, unless you have some mechanism of insuring that they have an amazingly high hematocrit, you are not going to uniformly achieve that minimum 50 grams if you're drawing a smaller donor.

That functionally, in fact, does solidify and go with 110 minimum.

DR. KLEINMAN: So if I understand your figures correctly then, the figures that you propose in standards are for the blood volume plus extra tubes, plus the tubes for testing. So it's not -- that 525 is

the bag plus tubes; is that correct?

DR. GROLIN: Correct. It's bag plus tubes. So people need to be aware of that.

DR. HALEY: And tubing.

DR. KLEINMAN: And tubing.

DR. HALEY: Yeah.

DR. KLEINMAN: My second question is, you know, the blood bags are marked for a volume plus or minus ten percent. I wonder what is standard practice. Do people these days try to hit, now that we've gone to the 500 mL bag, try to hit that?

I mean I know there was a time when people were collecting in 450 mL bags, that they would commonly go plus ten percent in order to get 495, but what about 500? Do people try to exceed that or not exceed that in practice?

MS. PAPENFUS: Well, I can answer a little bit of what I found in the survey, and that is that most of them were setting their scales to trip at 525 so that they did not ever go over the limit no matter how big the donor was.

DR. KLEINMAN: That would be 525 with the additional tubes. So really there --

MS. PAPENFUS: I'm sorry. Yeah, the scale trips with additional tubes they would really only draw

525.

DR. KLEINMAN: So they're really drawing about 490 or something like that.

MS. PAPENFUS: Four, ninety-seven I think it was.

DR. KLEINMAN: Yeah, and one other issue that was raised in the introduction was how people felt about low volume units, and I don't think that was addressed.

I mean obviously one wouldn't try to draw a low volume unit, but what happens if you do have a low volume unit? Should you be able to use it? Do you have to adjust the anticoagulant ratio? At what level is that unit still usable? Could you use that unit, label it appropriately and use it for pediatric transfusion when it's certainly good blood and shouldn't be discarded?

I wonder if there are any opinions as to that that might help the FDA out.

DR. HALEY: Our pediatrician, we'll start with you.

DR. GROLIN: Not only wonderful opinions, but there is a wonderful answer in -- do I sound like an advertisement for Standard Source?

In Standard Source where Gary Morov put

really an elegant historical review, citing both the Larry Button and a Rich Davie study which document the safety, purity, potency and efficacy -- I'm not sure about the purity -- but the efficacy of these low volume units, hence down to 300 mLs for 450 mL bag and, by analogy, there is no unique data by analogy down to 335 mLs for the 500 mL bag -- would be adequate.

And sure, at Boston Children's it's not rare that you have a -- I mean, as I said, pediatricians order in cc's per kilo, and instead of wasting a unit since who's going to use the other half of a unit, yes, we would often use the low volume units, and it's not making good use of people's gifts to discard them when they're perfectly good and have been shown to be so.

DR. KLEINMAN: So currently if one draws a low volume unit, I don't know whether I picked it up in your slides; are those generally used? Are they generally released?

MS. PAPENFUS: The majority of them from what I found out were tossed. They did not know what to do with them. They were below the magic 300 mLs. They were meant to be a whole unit.

DR. KLEINMAN: Right.

MS. PAPENFUS: But they didn't get enough.

They tossed them because the questions were -- one of the questions that came out of my survey was what do they do with that unit. Is it okay to use? Because the anticoagulant ratio was different than the one in --

DR. KLEINMAN: But, no, I'm talking about the ones that would be between 300 and 450.

MS. PAPENFUS: Those were used. They were labeled as low volume and used, yeah.

DR. KLEINMAN: One additional point I wanted to make with regard to the proposed revision of the hematocrit requirements is I think that one of the reasons the hematocrit was set higher for women than you propose is because of the possibility of cumulative donations up to five times a year and iron deficiency, not because of leaving them with a red cell mass that would make them anemic post donation.

So you really haven't taken that into account in these particular recommendations, and I think, in fact, if you look at the literature on this, maybe one should question -- if one is questioning the hematocrit limit and wants to lower it, maybe one should question the frequency of donation limit in women. Probably five times a year for a woman donor is probably more risky than taking a woman donor down to

11.5 or 12 grams two or three times a year, which much more simulates the usual donation behavior.

So I think that that's just one more variable to put in the equation, which is number of donations per year.

DR. HALEY: We find that women, of course, fail to be able to donate on hemoglobin five to eight times as frequently as men. I mean it's just a thing, that women have difficulty assimilating the iron, holding the iron stores, and producing enough red cells.

And so as it turns out, women are not able to donate as frequently with our current limitations because, again, they are deferred from donation. We hope they come back, but they're deferred from donation much more frequently than the men. And in some studies it's been as much as ten, 15 percent of the women presenting.

So, you know, I think the hematocrit or hemoglobin limits are set to protect the women, and you know, we could have debate on that. I think they do so. They certainly defer the women more frequently.

And I'm a little jealous of that 38 percent. Sorry.

DR. GROLIN: From the scientific

standpoint, I think it is worth saying that iron metabolism is far more complex than I would ever want to appreciate. Ninety-five percent of the iron that goes in your mouth is not absorbed, but the amount that is absorbed is actually quite variable and a function of your iron repletion status.

And your body is smart enough to know, those with hemochromatosis being possible exceptions, that when you're iron deficient you should take in more, but when you're iron repletes, take in less.

So, in fact, when you get a little bit iron deficient, i.e., when you're driving those women who have a hematocrit of 38 down to 36, who weren't iron deficient, they will, in fact, start to uptake more iron.

So it is a little complex, but I agree it probably is of less concern than a woman donates an hematocrit of 36 twice a year than a woman donates hematocrit at 38 five times a year. Then that, in fact, I would agree wholeheartedly. At the very least one certainly needs to address the issue of the amazing number of apheresis platelet deferrals due to this hematocrit requirement when we're not dropping people's hemoglobin in the least. That at the very least makes little physiologic sense

DR. MALLOY: I'm Dale Malloy from Jacksonville, Florida.

I don't carry a calculator, and I don't know the physiology as well as you do, but I have the sense that a 450 mL bag minus ten percent, which the anticoagulant allows collecting normally, is categorized as a standard unit of blood. Is that a safe assumption?

And so a woman who is 102 pounds in weight who wants to donate blood, I would ask the question: could we not draw, collect a reduced amount of blood from this light weight person that is in excess of 405 mLs, and collect, indeed, a standard unit of blood?

Do I need to ask the question again differently?

DR. HALEY: No. I'll tell you we've thought through this in the Red Cross system, and when we decided to go to 500 mL bags, we understood that we could no longer collect the people who were below 110 and do justice to them, and so any strategies that we had before we accepted the 500 mL bag as our standard, and it was very difficult to manage having two size bags on the mobile unit at the same time and then have to have two settings for all your scales and all that sort of stuff.

So we made the operational decision that we did not want to do that.

DR. MALLOY: That's a different answer.

DR. HALEY: So that's a different answer.

DR. MALLOY: The question --

DR. HALEY: We agreed that you could if you would use a 450 mL bag and only collect 90 percent of what you were able to collect. I think if we went through this same algorithm again, you would not be dropping this woman below 30 percent.

DR. MALLOY: And so that, in your view, could constitute a medically and scientifically sound practice without detriment to the person, to the donor.

DR. HALEY: Right.

DR. MALLOY: Assuming they meet all the other requirements, and this is yet not permitted by the FDA; is that correct?

PARTICIPANT: (Inaudible.)

DR. MALLOY: I understand, and I guess that is the question. There are a lot of healthy, low risk young people who would like to do that. Okay?

Thank you.

PARTICIPANT: Take it under advisement.

DR. SAYERS: Merlyn Sayers, Carter Blood Care.

This is a comment. I think if an outsider was listening to us they could be pardoned for thinking that the donor who is deferred with a low crit. is an individual on whom we have visited some ill health, and that is certainly not the case.

The individuals that are deferred with lot crits. that are being bled either a single unit or a double unit recently are many individuals who are reflecting the fact that their iron balance is of such a kinetic that they take longer to restore their red cell mass than any other individual might.

We're protected in the sense that tissue iron stores, be they in respiratory enzymes or wherever, are jealously guarded by comparison with hemoglobin iron. So the individual who might be deferred with a low crit. who is a regular donor is not an individual who is at any significant health disadvantage unless he or she is really an aggressive manual laborer because their tissue iron stores are retained.

DR. HALEY: I think the question here, just to make a comment on your comment, the question that I think is before us is: who can afford to give blood? I don't think we're trying to comment on their general health. I think we should be very careful not to take

from the person who cannot give it freely and maintain their good health.

DR. GROLIN: And it's also made more confusing by a recent series of studies in Circulation and others suggesting that from a cardiac standpoint a little iron deficiency might not be bad for you.

Now, is that due to the high rate of the hemochromatosis gene? And is that a little bit of iron depletion selectively protecting that subset and that is seen in the larger whole or is this a generalized phenomenon?

We don't know. There are places that would love to say, you know, "Donate blood. It's good for your heart." I'm a little reluctant to push that, but there's more than one study that does suggest that a little iron deficiency is good for you, and I can tell you from taking care of the thalycemics that excess iron is bad for you.

DR. SIMON: I guess I would just echo some of the previous comments. I realize there is a balance on the iron issue, but having studied iron deficiency in the past and from personal experience, people who become iron deficient and anemic suggest to their clinician possibilities such as colon cancer and you wind up having investigations such as colonoscopy and

the like. So I think you have to be cautious in terms of saying less iron is better for you, and come donate and get iron deficient.

And I guess the other issue that I would like, you know, perhaps giving Dr. Forrest a chance to comment, is there was some suggestion from the speakers from AABB and Red Cross and ABC that with regard to platelet donation we might move that up. I guess that was the implication because we allow people to donate such that in six months they can donate four times in a month, and in six months donate the 24 times. So why not allow them to donate 24 times in a year?

And the permissible plasma levels have been fairly well worked out, as Dr. Forrest indicated, and when you reach certain levels of plasma donation, the FDA has regulated with the requirement for physical exam and serum protein electrophoresis and the like.

So it seems to me with the amount of plasma being taken from these platelet pheresis donations one would have to tread very carefully in terms of moving up that allowance.

DR. FORREST: I would agree with that. It seems like where you're coming up against there is the line between the infrequent donor and the frequent, recurrent, what we think of as source plasma, serial

plasma pheresis donor, and I would suspect right now to get beyond that point you would have to deal with the perhaps the full source plasma regulations of physical exam and more detailed medical history at certain times than others, and some of the protein testing, serum plasma electrophoresis we did on an every four month basis because you take out larger volumes of plasma. That does have to become a concern.

Its' what impact are you having on proteins?

DR. GROLIN: And, in fact, my comment on the Web site was a direct discussion with Dr. Jong Hung Lee of the FDA. There was a particularly enthusiastic donor, platelet pheresis donor, who was inquiring could he not donate more than 24 times a year, and after discussion with Dr. Lee we both came to the conclusion that since this question comes up again and again and again, it's worth examining, but it's examining in the setting of a study that would measure exactly the sort of parameters that you're addressing.

MS. CALLAGHAN: Okay. Thank you very much.

Okay. We can start with our third section, which I'm sure will elicit a lot of comments. It's on cancer and should we defer donors, and moderating will be Dr. Toby Silverman, who is a medical officer in the

Department of Hematology.

And she's giving me work to do, too.

DR. SILVERMAN: That's because I'm supposed to be in another place right now.

My name is Toby Silverman. I'm a medical officer, now in the Division of Hematology in the Office of Blood at CBER.

I was asked to give this introduction on donor deferral for a history of cancer, and this is going to be a very brief overview, as the speakers probably know considerably more about this than I do personally.

Next slide.

At present neither FDA nor the plasma industry has enunciated a requirement for deferral of a potential donor because of a history of cancer. As you all well know, FDA is currently developing new guidelines for donor suitability, and hence the questions that will be asked and discussed today will form part of the consideration for these new guidelines.

Next slide.

FDA is proposing donor suitability standards that are designed to prevent a donor from being harmed by the donation process, and to help

insure collection and preparation of high quality blood and blood components, and as part of the standards will be included the following:

That donors should be in good health. The history should rule out exposure to disease, and behavior resulting in increased risk of communicable disease.

But I want to point out here the standard the donor should be in good health.

Next slide, please.

The proposed FDA language states that factors that may affect the health of the donor or the recipient or the integrity of the blood or blood component must be considered when determining general donor suitability, and again, these will include a history or symptoms of or treatment for an accurate or particularly chronic illness and a major surgical procedure.

Next slide, please.

Now, current practice in this area varies from center to center subject to individual physician discretion. For example, with regard to the potential bone narrow donors, NMDP health guidelines provide that individuals with the following may be eligible to be a bone marrow donor, that is, patients with cured local

skin cancer that is simple basal cell carcinomas or squamous cell carcinomas, or patients with cervical cancers in situ, all other forms of cancer being unacceptable for bone marrow donors according to the NMDP.

Next slide, please.

Now, what's the background here? The speakers that will follow me will elaborate in this area.

There have been scattered reports of cancers transplanted from one individual to another, very scattered reports of patient to surgeon transplants, and somewhat more transplant donor to transplant recipient, however.

Next slide.

There have been no reports of cancer transmission attributable to the administration of blood or plasma products.

In addition, a number of cancers now have prolonged disease free intervals with no evidence of metastatic disease.

Next slide.

Looking at protection of the donor, what might be the possible reasons for deferral of a donor for his or her protection? One is the development of

anemia or thrombocytopenia, deficiency of immunoglobulin, and last, most speculatively, progression of disease.

Currently there are no clinical observations to support the idea that blood or plasma donation has long term detrimental effects on the donor. Hence, the questions that will be posed to you today:

Should a donor with a history of cancer be deferred?

And if not, under what circumstances might such a donor be permitted to donate?

Now, the speakers that will follow me are as follows. No relationship, but with a great first name: Dr. Toby Simon, who is Vice President at Serologic Corporation, representing ABRA.

Dr. Bruce Newman, Medical Director for ARC Blood Services, interestingly enough representing AABB.

Dr. Merlyn Sayers, authorized official for Carter Blood Care, representing ABC.

I'm learning my alphabet here.

And Dr. Linda Chambers, physician at ARC Biomedical Services, representing ARC.

Thank you.

The first speaker is Dr. Toby Simon.

DR. SIMON: I'm privileged to participate and am delighted to have the opportunity to participate in looking at some of these donor suitability issues and recognizing when I asked why this was on the program that apparently the differences in approaches of different programs around the country has created some problems for FDA when the consumers or the would be donors call and wonder why they can donate in one place and not in another.

And as has been indicated, this has not been an area that has had uniform rules.

Now, I'm assuming that our concern here is that a donor with cancer might in some way affect the blood supply or might be in some way hurt by donating, and the reason we ask donors if they have a previous history of cancer is that they are more likely to have another tumor or metastasis or recurrence from a tumor they've already had than is someone in the population likely to suffer from cancer.

Obviously any donor who comes in to donate could at some time subsequent to that develop a malignant tumor. So would a donor likely have a malignant tumor come up about a week after donation? There's a likelihood, possibility of that happening with any donor, and of course, we're assuming there's a

greater possibility with people with previous cancers.

I tried to pull some data out from the medical literature that might help us, and some of this incidence data is very difficult to deal with. So this was a simplified way of putting it from the cancer textbook, and a lot depends on the age of the donor that you're dealing with.

In the plasma industry we tend to deal with young donors, and the likelihood of somebody in their youthful years developing a tumor in the near future is fairly low. This increases as one goes into middle age and gets to larger likelihood as one gets older.

And this is particularly, I think, relevant to the whole blood community because of the emphasis on recruiting older donors. You're getting into a situation when many of your donors with no history of cancer have a likelihood of developing a tumor at some near point in the future that probably approaches the younger donor with a history of cancer.

So if you had to choose between a 35 year old man with a history of testicular carcinoma that had been apparently successfully treated and a 70 year old man or woman who has no history of cancer, that likelihood may be somewhat similar.

I actually tried to get that data, but it's

very difficult because it's so different for every tumor in every stage and every form of treatment. So one is immediately struck by the paradox if what you're trying to do is prevent drawing someone's blood who might subsequently have a tumor in the near future in terms of whether asking a history helps that much versus someone who doesn't have a history.

We can have the slides off for a minute.

The question that one, of course, is posing always, as has been very well stated, is is there a harm to the donor. Is there a harm to the product?

And I've always taught that with this particular deferral criteria that what we're concerned about is the donor and his health or well-being because there's no indication that transfusion of blood components or blood derivatives can result in transmission of tumor or of any kind of malignancy.

And also when we're speaking about malignancy, I am eliminating the basal cell carcinomas, the squamous carcinomas, and carcinoma in situ of the cervix, which are generally fully cured simply. So I'm assuming that most programs would accept that as acceptable and not include it in its definition of cancer that we might exclude, and we'll see if everybody buys into that distinction particularly these

days, I might add, with the medical legal problems that those who read Pap smears have. Women with atypical smears having various procedures done is very common, and one I don't think would want to get into deferring all of those people.

Several years ago I got a frantic call because one of our donors had been diagnosed with leukemia within a week or so after donation of whole blood, and several of his -- two of his components had been already administered to other patients, and I wanted to reassure the people that they didn't have to worry about the recipients coming down with cancer.

And at that time I found an old study in the literature where an investigator actually tried to transmit tumor, and I thought it was very useful information, and I think it's summarized on the next overhead.

This was a study which appeared in a Journal of Lab. Clin. Medicine in 1945 by an Australian researcher who worked very hard at trying to transmit tumor, and he did it in several different ways which I've tried to summarize: injection of spleen taken from autopsy, given subcutaneously; injection of material, various pathologic material intravenously; and in transmission of one form of leukemia into a

patient with another form of leukemia.

And what he did is he had patients who came to autopsy. He very quickly took their material and then injected it into other patients who had a life expectancy of two years or less. This, of course, struck me as the kind of research that we'll never see done again and probably shouldn't have been done back then.

(Laughter.)

DR. SIMON: But just to give you an example, in one of his protocols a woman 46 years of age died of acute myeloblastic leukemia. Her white cells were 800 per cubic milliliter at the time of her death. Five different patients with other kinds of tumors got two cc's subcutaneously 20 minutes after her death from spleen that was injected, and then he did various alterations of this.

Some of the spleen was kept for one hour at four degrees and then injected. Others were kept overnight and injected actually into 19 different people, and then eight people received myeloid leukemia cells from somebody who died subcutaneously. Others he gave them intravenously.

And then he had the patients who already had leukemia that he gave a different type of leukemia

to, and it's very instructive to read. He worked very hard to try to transmit directly man to man a tumor, either by one or another kind of injection, some of which mimicked transfusion and was unsuccessful in doing so.

Interestingly, in his conclusions he was a great enthusiast for this theory, and he concluded that he had not shown that you couldn't do it, but that there was obviously something wrong with his methodology by which he was unable to cause this transmission to occur.

But I was very impressed that someone who worked so hard with a number of different mechanisms to transmit tumor from one person to another was unable to do so, and he got autopsies on virtually all of the people who died. It turned out he was right. They all died within about -- I think the latest was 26 months, and with a couple of exceptions he got autopsies and hunted for any evidence of transmission of tumor and was unable to find any.

And in the next slide, in his paper he reviewed what was known in the past, and actually there had been a number of cases which he cited which you can read here, one of which is an accidental transfusion from a leukemia patient, and then other people who had

done experiments trying to inject tumors, one to another, and had failed to do so.

So at least up to that time it appeared that one could not transmit tumors from one person to another.

About the best -- we can have the slides off for a minute -- about the best experiment that I'm aware of at the present time or more recently I should say were the multiple transfusions from patients with chronic granulocytic leukemia of their granulocytes into recipients in the early days of granulocyte transfusion therapy, and of course chronic granulocytic leukemia is a stem cell disease. So presumably within that transfusion -- it was a clonal so within that transfusion were stem cells capable of setting up and starting a new tumor, and there were no incidents of transmission.

Now, lest you're not convinced by what I've indicated, that there is no danger to the recipient from a donor who might develop cancer, have cancer, I think Dr. Newman I see from his slides has an even much more exhaustive review of the literature here, and hopefully you'll be convinced after seeing his data.

One more slide I think is of interest and is very up to date. At a just recently concluded AABB

national meeting there was an abstract from a group in Kansas City that did a flow cytometry analysis of donors and found out that many donors are walking around with B cell ALL in their blood or CLL in their blood, have the B cells present, and they calculated that there would be 65,000 donations per year in the United States that would have this particular neoplastic cell circulating in the donor.

They actually suggested that perhaps this is actually greater than the risk of transmitting a viral disease, and they suggested that perhaps this is what we should be screening for, but I drew the opposite conclusion.

This has obviously been happening year after year after year with no evidence or no reports that we are causing tumors by transmission of these cells.

Slides off.

So I have drawn the conclusion, which I guess we'll be discussing with the other three speakers and with the panel, that there really is no risk to the recipient from either a red cell platelet transfusion or from a plasma derivative of the transmission of a neoplasm, of a malignancy from one person to another.

This, of course, does not necessarily take

into account some of the cases that have occurred. We know that cancer does spread hematogenously, and that there's always concern at surgery if cancer cells are distributed and are left in that they can propagate and cause metastasis.

But I think that the actual direct transmission into the blood stream by a transfusion has not proven to be a route by which cancer is transmitted. So that we do not need, in my opinion, an exclusion for donation for people who have had a previous malignancy based on concern about the recipient.

So that takes us to the next issue, which I assume has always been the matter of most concern: do we need to protect the recipient?

And here I think that what we're concerned about is that -- or do we need to protect the donor? Excuse me -- and here I think what we are concerned about is that someone who has had a malignancy will donate and at some time shortly thereafter will have a recurrence, and that their ability to be treated successfully or to fight the tumor or whatever will be reduced because of the fact that they've donated.

Somebody who's anemic would obviously be at some disadvantage in starting chemotherapy or going to

surgery for tumor. Perhaps one could make the same argument about thrombocytopenia from platelet donation, and there is the argument from long term plasma donation that immunoglobulin depletion may be linked to immune surveillance and could in some way impair an individual's ability to prevent a metastasis or recurrence from happening.

However, in the case of the plasma donation, as has already been shown, there's really no clinical data to suggest that it causes an effect, and we also know from studies that have been done in plasma donors that there's a change in the lymphocyte composition, and there's a reaction to the immunoglobulins and more immunoglobulin producing cells are developed so that the individual regenerates that capability.

So it seems not to be obvious that a donor who had donated plasma, platelets, whole blood would be significantly disadvantaged if they should have a recurrence.

Now, when we look at patients who have malignant tumors, a couple of things that we need to keep in mind. One is that the five year survivals are much enhanced and more and more people are being treated successfully, and these are some recent data.

Unfortunately there's a difference between white and black people. In the lower five year survival, black people, 42 percent, and 58 percent in white people. So there's good survivals in patients who have been treated for malignancy.

Another factor that we can keep in mind is the recent textbooks still say that for many cases or for most instances a five year survival is tantamount to cure. So this gives us one guideline that we could use if we wanted to be somewhat conservative in accepting people who had had a previous malignant tumor.

The major exceptions to this are head and neck tumors and breast cancers, mainly because of a second tumor, and with breast cancer we have been concerned primarily about a tumor appearing in the opposite breast, and now with the conserving surgery that is used, the use of lumpectomies, there's also a risk of a tumor, another breast cancer in the remaining breast.

And we also know that breast cancer has a major chance of metastases many years out, and that the five year doesn't necessarily mean free of danger from metastatic disease.

However, looking at the more recent

protocols for breast cancer, it looks very promising that that risk of metastasis has been reduced, and it's hard to kind of summarize, but in the cancer textbooks where they talk about all of the different cases where the receptors are positive or negative or it's one node or so many nodes and the different treatment protocols, for many of the protocols they're reporting 90 percent disease free survival up to ten years. So the five year number is becoming better for breast cancer as well.

And the head and neck cancers, the chances of a recurrence particularly thyroid cancers are what's in mind.

So from all of this, if we put on the last slide, I've tried to come to some terms with what our approaches might be, what we might recommend to FDA or utilize in our own organizations, and I've lifted these in order from the most permissive to the most restrictive.

Given the excellent record of treatment for cancer and given the fact that we're drawing older donors in the whole blood side of things and that any of our donors could possibly get cancer, one could simply eliminate all deferral criteria for cancer, drop even the AABB's requirement, and simply ask about

recent illness, major health problems, and make a donor suitability decision based on the answers given.

So if someone says, "I just stopped my chemotherapy last week," you might defer that person. If someone says, "I haven't had any recent problems. I had a cancer many years ago," you might accept that person.

The second option is to ask about a history of cancer and accept donors who appear to be disease free, and this is the one that I tend to favor, and it has a bit of a bias from the plasma industry point of view.

All plasma donors, just to remind people who may not be familiar, at the time of their first donation if they're going to be a frequent plasma donor are subjected to a history and physical examination either by a physician or by someone substituting for that physician who's been appropriately trained, such as a nurse.

And at that time they have a more extensive history and at least a baseline physical examination that includes lungs, heart, abdomen, and lymph nodes, and a brief head and neck exam, and a brief neurological exam.

So one has the opportunity to do a fairly

extensive, more in depth survey, and if someone has a history of cancer, to ask a number of questions, delve into what it's all about, the likelihood that the individual has been cured and is to remain disease free.

In addition, the plasma donor is coming to a fixed site. So if you want to get more medical information, if you want to call and speak to their doctor, it's not a major problem to defer that person on that day, have them come back two or three days later when you've been able to put all of that together.

So given the medical direction that's present and also even if a non-physician is doing the history and physical, the rules for plasma donors that it's required that a physician be available to discuss with that person the situation and to make a decision.

So I think we have the opportunity to use medical judgment to determine donor suitability in individuals who have a previous history of tumor, and with so many patients with early stage Hodgkin's disease, testicular cancers, many other tumors having cures these days, this seems like a reasonable approach.

In the whole blood side of things, you may

be doing a blood drive 200 miles away from where you are, and it's either you accept that donor that day or you next see them eight weeks later or whatever, and you may want a more clear-cut provision that people can use very simply, and I would suggest that the five year rule is a pretty good one in that situation; that if you don't want to delve further into the person's history, get a physician involved, get medical history, that the simplest thing may be to accept five years cancer free, that is, someone whose tumor -- who appears to have been free of tumor and any recurrence for at least five years could then be acceptable as a donor.

The most restrictive would be to exclude donors with a history of cancer. I would hope that we wouldn't be pushed to do that. I don't have any data from the plasma industry. We don't have data readily available on how many people we exclude from this, but since we deal with a young donor population, it's likely that it's a relatively small number of individuals. It might be much larger in whole blood, particularly with older donors.

Even though this exclusion may be relatively small percentage wise, I think we are beginning to see with both plasma and whole blood that

there could be significant restrictions on about ability to treat patients based on supply and for us not to have some ability to accept patients who have had a history of cancer with so many of these patients being now disease free, being successfully treated, and with the fact that any of our donors could come down with a malignant tumor, and we're simply screening out cancer patients who may have a slightly higher likelihood of doing so.

It seems to me unduly restrictive not to allow any cancer patients or individuals with a history of cancer treatment to donate or with a cancer diagnosis. So that seems to me to be unduly restrictive.

So I think if the FDA feels that with its new regulations it needs to have something specific, I would argue for having something that allows a physician determination of donor suitability, and if the whole blood -- and I think one compromise solution might be to say individuals could be accepted how have a history of cancer if they've been disease free for five years, and to allow a physician override if they have been disease free less than five years, and that would kind of combines numbers two and three.

This would also be an area where I think

the FDA could leave it to individual centers. There's not really any significant data in my view to suggest that there's significant harm to donors or significant harm to patients if we do not elicit a cancer diagnosis and don't act upon it.

So I think that there would also be a viable alternative of the FDA not placing a restriction and even the AABB removing its current restriction and leaving the decision to individual organization. Those organizations could make the judgment based on their own medical oversight and how much they have.

But I recognize that there may be an anxiousness to have some kind of similarity across the country, some kind of uniformity, in which case I would argue for some combination of options two and three.

MS. CALLAGHAN: Next we'll have Dr.l Bruce Newman present his point of view.

DR. NEWMAN: Okay. Thank you very much.

Thank you to the AABB and to the FDA for giving me the opportunity to come here and speak to you today.

My expertise is basically from being a blood bank medical director and also having an interest in blood donor suitability issues.

Our topic, of course, is history of cancer

and blood donor suitability.

Next slide.

And I'm going to cover the topic really in two parts, and the first part I'm going to provide background on donors with a history of cancer, and I'm going to cover deferrals, a little bit about deferrals in general, and then deferrals for cancer at American Red Cross Southeastern Michigan Region, which is basically the metropolitan area of Detroit.

And then I'm going to give you the results of the surveys of seven blood centers for cancer donor suitability criteria, and this includes also systems and represents about 60 to 65 percent of blood collected in the United States.

I also looked at those seven blood centers or blood center systems for what is their cancer retrieval policies, and then I'm going to quote to you what the AABB position is on cancer. That's the first part.

The second part I'm going to look at more of the real issues concerning donor suitability criteria. I'm going to look at the donor and also the recipient risk, and quoting some of the same, some additional data concerning that that Dr. Toby Simon just presented also.

And then if we want to go further and determine recipient risks, I have a couple of suggested possible studies to do that, although they're quite tedious.

And then finally I'm going to discuss what the possibilities are for donor suitability criteria.

Okay. The next slide.

Well, topic one, I'm going to look at deferrals in general, and what I have to say about deferrals is they are very negative, not just that you defer the person, but you also affect the persons even deferred for a minor, for let's say a short term, temporary reason is less likely to come back and will donate a lot less blood than people who are not deferred.

Next slide.

And there's two lines of evidence really to show this. This is a study that we did at our center back in 1998, and titled "The Effect of Short Term Temporary Deferral on Future Blood Donation," and what we did was we looked at 2,793 deferred donors who were deferred in the first quarter of 1993 in our blood center, and they were deferred for what we call short term, temporary deferrals, things like sore throat, cold, elevated temperature, not feeling well, or

elevated blood pressure. Really things that just affect you that day, and a few weeks later you're fine and can donate.

What we then did was we matched them with nondeferred donors who had not been deferred, and they were matched for being the same age, same gender, and donating around the same time.

Next slide.

And then we followed them in the computer system for the next four and a quarter years, and we looked at the percentages of both groups that came back to donate and how many donations they gave, and what we found was that the controls, 80 percent of them returned versus those who had been deferred for those reasons I suggested. Only 62 percent returned so that actually the controls were 29 percent more likely to return during this four and a quarter year period.

More importantly, the controls donated 80 percent more blood. If you defer somebody for a cold or a sore throat, this is what you're going to see over a period of time in this kind of a group. Thirteen thousand eight hundred units were donated by those who were not deferred versus 7,600 by those who were deferred.

Next slide.

So the conclusion here is really that deferrals are negative and they do affect future donations and the amount of blood that we're going to get.

The other line of evidence is when you look, there have been several little studies done on first time donors, and they've also found it even more negative. Newnan (phonetic) in 1981 looked at first time deferred donors and zero out of 64 returned.

Evans in 1981 looked at first time nondeferred donors, and 97 out of 233 returned, or 42 percent, but they had in their small group of deferred donors only -- actually zero out of 14 returned.

And Pilovin or Glavin -- I'm not sure how to pronounce it -- in 1987, they found that first time nondeferred donors in their time period, 27 percent returned versus first time deferred donors; only three percent returned.

The bottom line here is deferrals are negative for everyone, but even more so in first time donors.

Next slide.

Now I'm going to turn our attention to cancer. I'm going to look at cancer deferrals in our region, and I think this is pretty much representative.

I can't say that for such, what's going on in the country, but it probably is very representative of what's going on in the country.

Out of 137,000 donations, 335 were deferred for cancer. That's about a quarter of a percent, and when you look at what percentage of our deferrals were due to cancer, we have about 8.5 percent deferral rate in general, and only a quarter percent were for cancer, so only represented about three percent of our deferrals.

So cancer in general is not a major cause for deferral, and it's not a major part of our deferrals, and any liberalization that we can do among this group will certainly make those donors happen, but they're not going to lead to a large increase in our donor pool.

Next slide.

I did do a survey of seven regions and systems, and these blood centers and systems represent 60 to 65 percent of the blood collected in the United States, and what I found was that donor suitability criteria really are not that much different across blood centers. Whereas retrieval policies are quite different.

Let me explain this slide. It turns out

that for hematologic cancers, things like leukemia, lymphoma, and multiple myeloma, everyone is giving those potential donors an indefinite or permanent deferral.

With systemic cancer they're requiring in most institutions a five year deferral from the time of the last treatment, and that assumes that there's also no recurrence of disease during that five years.

Slight differences. One institution has a ten year deferral period. One has both, and one institution has a chemotherapy role such that if you did get chemotherapy for your tumor, then you have an indefinite or permanent deferral.

In terms of biopsies where you're waiting for results, everyone sees it as a temporary deferral.

Skin cancer, non-melanoma skin cancer, everyone is pretty much in agreement that those are okay assuming it's been excised and it's been healed. Slight variations on both sides. One institution even takes melanoma in situ.

Finally in situ carcinomas. Some institutions are accepting all such cases. Some just limit it to the cervix and accept those.

Next slide.

Now, in our institution, we looked at 143

cancer deferrals, and we broke them down into these different kinds of categories, and we're a Red Cross institution. Twenty-five percent of our deferrals are indefinite or permanent, and that can be broken down into six percent for hematologic cancer, 16 percent for chemotherapy. We're the institution that has that rule, and three percent for recurrent cancer.

If you're in a non-Red Cross center, then you would not have that 16 percent, and you would only have nine percent fall into this category.

Five year deferral, 59 percent of our deferrals in our center are five year deferrals because of systemic cancer. If you were in a non-Red Cross center, that 16 percent would go into this category, and it would be 75 percent.

Finally, temporary deferrals. Sixteen percent, a little bit because of skin cancers, non-melanoma skin cancers, but mostly because of biopsies that are pending.

Next slide.

When you look at retrieval policies, you get a lot more variation. There's two kinds of retrievals that could occur. One is when there was a donor who had been donating despite the fact that he had a history of cancer and shouldn't have been

donating. That's the first category.

And then the other category is where a donor has been donating and was certainly eligible at each donation, and then about a month or two after the last donation comes down with a diagnosis of cancer.

So looking at these two situations with the inappropriate donations, some institutions are not notifying. They're not concerned about it, and if they have in-house donations, they will destroy those, but that's as far as they go.

Whereas others can be at the other end of the spectrum, notifying everybody and destroying end dated or those units that could still potentially be around, and then some people are in between. So it's a little bit all over the place.

I think in part this reflects -- when I spoke to the individuals, they really had to think about what their policies were because they don't come across it enough times to really know it off the back of their hand.

And also in part, people do not have readily access to knowledge as to whether really cancer can be transmitted or not, and therefore, it reflects their own policy as to whether they want to be very conservative or not on the issue.

Donations just prior to diagnosis. Well, if you're not that concerned that cancer can be transmitted, then what's the point of going back and retrieving the unit? Whereas others would go back one or two months, possibly even longer to retrieve units. This is when the donor has been donating, and subsequent to the last donation they find that he or she has cancer.

Next slide.

Okay. Now, what is the AABB's position on this issue? If you look in the latest edition of Standards, 19th edition, which came out in 1999, under B1.700, under medical illness, it states, "Prospective donors with diseases of the heart, liver, or lungs or with a history of cancer or abnormal bleeding tendency shall be excluded unless determined to be suitable to donate by the blood bank medical director."

That's what AABB has to say about it. To me this means that it's really up to the organization themselves to set up the policies to deal with this issue.

Next slide.

Okay. That is the background on donors with cancer, and now I'd like to get into risks, risks for the donor and risks for the recipient of a unit

that has or could potentially have cancer in it.

In terms of the risk for the donor, I think personally the risk is marginal. The people that come to our door are self-selecting themselves as being in a more healthy state and, in general, would be accepted if we did not know about that history of cancer.

I think this applies to the overwhelming majority of cases that we see. So to me I don't see a history of cancer as being a real significant donor issue.

Also it's a fact that donors with cancer are donating blood. Why? Well, it's very simple. They don't know they have cancer, and specifically if you're taking men over the age of 50, we do know that a high percentage or a certain percentage of those men will have cancer, and that increases as they increase in age.

In fact, someone has said that if a male lives long enough, he will eventually develop prostatic cancer.

Next slide.

So let's look first at the recipient risk, which I think is the crux of the issue: can you transmit cancer from a donor who has cancer to a patient?

And to our best knowledge, there have been no reported cases of cancer that's ever been transmitted from a donor to a recipient.

Now, let's look at the evidence.

Next slide.

And I think the best evidence is in those situations where transfusions are -- let me say this. The best evidence that we have available is those -- are those transfusions that have occurred from leukemic donors to blood recipients.

Next slide.

And if one looks at all of those cases, you have 72 such cases. The majority of them were done by Thiersch, et al., in two studies, one in 1945 and one in 1946, and we're talking about 62 cases. I think Dr. Simon has very nicely presented what at least the first study, but I'm going to present a little bit about that again.

Bierman, et al., had seven cases. What he was doing was these were cross-transfusion studies. He had seven leukemic patients, and he had relatives come in as volunteers, hook them up vascularly to each other, and used the volunteer relative to try to clear the leukemia cells from the patient.

He found that it didn't really help the

patient, and none of the donors ended up leukemia either.

And then you have some cases studies which also for whatever reason sometimes it was an accidental -- it was a donation that later the person came down with cancer or other reasons also did not transmit cancer.

Okay. Next slide.

This is the 1945 and 1946 data that's coming from Thiersch, et al., out of Australia, and he had leukemic donors and volunteer recipients, and I would say almost all the recipients were cancer patients themselves where the life expectancy was not expected to be that long. Some of them did live as long as two years.

And what he did was if a leukemic donor died, he would take out the spleen. In this particular donor, he had all kinds of preparations, and he would give it to several recipients, and he did a couple more donors, another three donors. He did it to other recipients. He used intravenous use of blood. He used a lymph node trying to mash that up and see if it could be transmitted that way, and in none of these cases did the patient end up with leukemia.

And some of the follow-ups are as long as

close to a couple of years.

Now, since that didn't succeed, he came back in 1946 and did another study, and in this study what he did was he took bone marrow from the donor and put the done marrow into the sternum of the recipient, did that in 11 cases, and none of those cases also developed cancer.

So the summary here is that in these 72 recipient where they tried to give the leukemia in many of them by subcutaneous injections of one type or another, intravenous injections, or even by direct bone marrow; none of the patients developed leukemia.

Next slide.

Another experience that we have is the CML experience where they were using CML patients as donors because they have tremendously high white counts, and the goal was to treat patients who had severe septic infections and had no neutrophils. So the goal really was not to see whether they were going to get leukemia. The goal was to treat infection, and most of the studies -- when we talk about that, some of the studies do comment on the recipients as to whether they developed leukemia or not.

So you have a whole host of studies. Mainly it was done in the '60s and also the '70s. By

the '80s people were getting more into using regular donors as a source of white blood cells.

Next slide.

So in these studies you're having hundreds of patients that were transfused. The dosages they're being transfused with are very high numbers of CML white cells, generally between five and 20 times ten to the tenth. Normally the accepted minimum or accepted standard is one times ten to the tenth. So you can see it's very high.

Some of these donors went up to as high as 120 times ten to the tenth. You can really see very high dosages, and for infections they were actually pretty effective, but none of the patients developed CML. That's the significant point.

Now, generally speaking the follow-up was short because people needing these types of transfusions were not in good shape to begin with, and so it generally was not past a year.

What they did note in a few cases was that there was engraftment, temporary engraftment of the CML cells into the recipient for up to about two months, but not past that, and there was very little evidence in these studies of graft versus host disease or graft versus leukemia.

I should add there was another recent study in Transfusion in April by Vargas in which they accidentally transfused -- well, they didn't accidentally. They transfused a donor who one month later or a few weeks later developed CML, and they followed the cells in the patient, and they found that the cells were there at about two and a half months, but was not there at six months. So this is pretty much in the same ball park. Two months engraftment or two and a half months is pretty much to say.

Next slide.

Another study where you're talking about direct transfusions is this study by Greenwald, et al., which is buried in the literature, called "Morbidity/Mortality Among Recipients of Blood from Pre-leukemic and Pre-lymphomatous Donors," and it's in Cancer, 1976. This was done in New York State by the Department of Health.

And what they did was they looked at their registry in New York of hematologic malignancy patients, which was 7,422 patients in this registry that were gathered between 1950 and 1969, and then they evaluated their blood donations.

Next slide.

And unfortunately only 211 could they find

records of having had donated blood, and this is essentially because the blood center does not keep records forever, especially of donors who are not donating, and these people have been entered between 1950 and 1969. So this is due to the fact that the blood center didn't keep records on these people for a great length of time.

And in the end, they only had 54 donations and 105 blood recipients to follow. So they lost some additional donations because the hospital didn't have the records.

But this is what they followed: 54 donations. You see very low yield of something to follow, but they followed it anyway.

Next slide.

And another limitation in the study was the fact that the interval between the donation, the last donation and the time that they were diagnosed was on average about five years. So pretty long interval.

So the question is: did they even have cancer when they had made that donation? So in many cases probably not. About 43 percent were less than three years.

Ninety-seven percent of the recipients were followed up. The mean follow-up was seven years, and

none of the recipients developed a hematologic cancer.

Next slide.

Follow-up was not that long when you look at the total, about 740 recipient years, and it takes -- here's the third limitation to this study -- it takes 4,400 recipient years before one hematologic cancer develops in the general population. So if you really wanted to do a good study, you would probably have to have a much larger number. I'd suggest it would be something like 4,000 recipient years where you would expect to see ten cases, and then you could compare to see if you had more or less than that number whether it was statistically different.

Next slide.

Okay. That is the best data I think we have in terms of recipient risk, but we have some other data, as well, which I thought I would present, and that is we have the interoperative autologous blood collections in cancer patients, and we have transplants with cancer versus blood transfusions with cancer.

Next slide.

Hansen, et al., in some very recent work from 1995 and 1999, with some very sensitive techniques to detect cancerous cells found that in 61 cases of cancer of various types where they were doing surgery

on the patient and using salvage, that really cancer cells are really quite frequent, in almost 90, 95 percent of the cases. Fifty-seven out of 61, they could find cancer cells in the operative field.

They also looked at blood taken from the patient at the end of surgery, and in about a quarter of the cases they could find cancer cells in the peripheral blood as well.

They show that these cancer cells are also viable, that they were clonogenic, meaning they could grow cell cultures; that they were invasive using in vitro tests; and that they were tumorigenic, meaning that if you injected them into mice that was immunosuppressed, they would go into a tumor.

Some background just to say that these cancer cells are present, and they're viable.

Next slide.

There are several studies which have looked at surgeries comparing those which they did salvage basically in a patient with cancer versus those in which they didn't do salvage and looking at recurrence rates, and basically you have urologic cancer, several studies, but it's all one group in Florida. Hepatic cancer, you have two groups. And cervical cancer, you have one group.

And in none of these studies could they demonstrate any differences in recurrence. Well, the problem with these studies is you're talking about small numbers of patients, between 30 and 80.

Next slide.

And, therefore, if there was really a dramatic difference, you would see it, but small differences, 20 percent differences, you're not going to see those types of differences.

Next slide.

The other situation which people often sometimes talk about is transplant situation, cancer and transplanted organs. Up through 1991, there were 130,000 transplants, and 164 of those transplants involved a graft that had cancer in it and was unknown to the people doing that transplant, about .13 percent. Most of these grafts were kidneys, 152, but there were also six livers, four hearts, one lung, and one pancreas.

So now you're transplant a graft that has cancer in it, and what they find is that when you transplant a graft, an organ, a solid organ that has cancer, that in 44 percent of the cases the patient developed cancer, 72 out of 164.

Next slide.

Of the 72 cases with cancer, the cancer was limited to the graft in 30 cases, or 42 percent. Seven percent showed local invasion outside of the organ, and 36, or almost half or actually a little bit more than half had metastatic disease.

Next slide.

Patients with metastatic disease, in some of the cases they were able to cure them, about a little bit more than a quarter. What they did was a nephrectomy, and they stopped the immunosuppression, and then sometimes in a few cases they gave chemotherapy and radiation, and they were able to get rid of the cancer in about a quarter of those patients with metastatic disease.

In almost three quarters, however, they did not survive, and this was despite the fact that they did do the treatment in at least ten of those cases.

Next slide.

So if cancer is in the graft, you're going to have about a 44 percent transmission rate. Fifty percent of the transmissions will end up with metastases, and two thirds of the patients with metastases will die.

Removing the kidney and stopping the immunosuppression will be successful in terms of

treatment for some patients.

Next slide.

But I think we're talking about two totally different situations, and this slide compares the two situations, where we're talking about cancer in the blood in a donor who has cancer versus cancer in a transplant.

In the blood, the cancer cells are in the peripheral blood. Here the cancer cells are already engrafted in the tissue or organ.

Here we have the low cancer load. Here we have a high cancer load.

Patients who are receiving blood generally or I would say almost always are not on long term immunosuppressive medications, whereas transplants are always on long term immunosuppressive medications.

And here we see no case reports, and here in the transplant situation, the latest data that's out there that I'm aware of, about 117 cases, case reports as of about 1997. So I don't think this situation is applicable to blood transfusion.

Next slide.

Well, we talked about what is available -- to determine what is available in terms of seeing whether there is recipient risk, and basically we have

not seen transmission even when they tried, but if you're not satisfied with that, if you want to see whether there's some kind of low risk from transmission of cancer cells in blood, then I have a couple of studies to suggest.

One study is to look at cancer deferrals, and when you have a cancer deferral, evaluate whether there are any blood donations within the previous year, and then go back and follow those components to the hospitals and determine who the recipients are and follow those recipients.

This has many limitations. Doing this kind of a study, you're going to, first of all, have many cancer types. You're going to need really large numbers, and it's going to be difficult to get follow-up on the recipients.

Next slide.

Another possible approach would be to go to cancer donor registries where you can get cancer patients by diagnosis, take those subjects, enter them into the blood center data banks to see whether any of them had blood donations within one year of their diagnosis, and then again, follow up on those components, identify the recipients, and follow those recipients.

Again, this is going to be tedious. We don't know what kind of yield it would be, and it's going to be, I would assume, difficult to get follow-up on the patients, but it does allow you to look at specific cancers. So it would have that kind of an advantage.

Next slide.

Okay. The last point is blood donor suitability criteria for cancer patients, and here I think we have two issues. We have what we know about the science, and the science suggests to the degree that the data is available that you cannot transmit cancer to recipients.

And then we also have to take into account the perception of the public, and the question is: will the public want to get a donation from somebody who has active cancer? And my answer is I think not.

So those two factors in mind, let's look at what today is the most popular approach to dealing with cancer patients, and I think it's pretty uniform, not exactly uniform, across blood centers.

Next slide. Sorry.

But basically indefinite deferrals for hematologic cancers; five year deferrals from the end of treatment for solid, systemic cancer if there's been

no recurrence, except non-melanoma skin cancers after excision and the lesion has healed.

Next slide.

Except in situ carcinomas, at least the cervical carcinoma in situs; temporary deferral for biopsy results, and do not base donor suitability on the type of treatment.

Okay. I think this is a reasonable approach personally. I think it allows a space of time where the person has not had -- the donor has not had cancer, and therefore, I think they would be in agreement with anyone in the public being able to say to them that you're not getting a donation from somebody who has active cancer.

Next slide.

If one wants to be more liberal, then a possibility would be to decrease the deferral period from the end of treatment to only two years for solid, systemic cancers, and I just chose the two. It's a very arbitrary way in which it was done, but allows a period of time in which a person has not developed the recurrence of their disease, and to possibly set deferral time period for at least some of the hematologic cancers like Hodgkin's lymphoma.

Next slide.

In summary, cancer deferrals are not a major cause of deferrals in the whole blood industry. Most cancer deferrals are due to systemic cancer.

Blood donor suitability criteria are fairly similar across blood centers, but retrieval policies vary.

There's no transmission of cancer or there's never been a transmission of cancer from a blood donation that has ever been reported, and the evidence in terms of direct transfusions of blood from leukemic donors -- basically direct transfusions of blood from leukemic donors has not resulted in long term engraftment or development of leukemia in patients.

It may be possible to gather large amounts of data to better determine or to be more definitive to determine if cancer can be transmitted via blood.

And I think the present blood donor suitability criteria as I've just outlined are adequate. If one wants to -- sorry. Next slide and next slide -- if one wants to go past that, it's possible perhaps to shorten the deferral period for systemic cancers and to set a specific set time period for some of the hematologic cancers.

Thank you.

MS. CALLAGHAN: Okay. Let's take a break and be back here at 20 minutes to four.

(Whereupon, the foregoing matter went off the record at 3:22 p.m. and went back on the record at 3:43 p.m.)

MS. CALLAGHAN: If I can get everybody to sit down, maybe we can actually finish on time. I guess not. Do I need a gavel?

Should I just say, "I'm the FDA and you'd better sit down"?

PARTICIPANT: There's a reg.

MS. CALLAGHAN: There is a reg. You will sit down.

Okay. Our next speaker on this quite controversial subject is Dr. Merlyn Sayers.

DR. SAYERS: Many thanks for this opportunity to say something on this topic, and I think it's wryly amusing that it's only a week since that Institute of Medicine report which suggested that something like 98,000 hospitalized Americans could die because of some medical error, and even if that's a tenfold hyperbole, that risk so dwarfs the risk of any transfusion transmitted mischief, and yet here we are discussing what steps we should take to prevent that which has not happened.

(Laughter.)

DR. SAYERS: This is to reveal again my affiliations. You'll be gratified to hear that I spent the break eliminating something like a dozen of my overheads.

There is a very limited body of information here, and for me to go any longer than the five minutes that I am now planning to talk, even six minutes I'll begin to sound like a hollow echo of Dr. Simon and Dr. Newman.

I would say though that I am a trustee of ABC, but this is not a position statement of America's Blood Centers.

A reminder then of where we were, the uniform donor history questionnaire. Interesting that this actual stipulation does emerge in the criteria for the protection of the donor section, and let me read it again.

"Prospective donors with a history of cancer or abnormal bleeding tendencies shall be excluded unless determined to be suitable to donate by the blood bank medical director."

And rather than go over what Dr. Simon has already said about risks to the donor, I think it is very, very difficult, indeed, to reveal that the donor

in this set of circumstances is at any risk.

What we did, creak, groan, was a survey of some 62 ABC centers which account for something like 50 percent of the national volunteer whole blood donor collections. We surveyed that group with two questions, and these were the two questions.

Do you accept any donors with a history of cancer? And if you do, what cancers are acceptable and under what circumstances are those cancers acceptable?

So we'll briefly -- and I emphasize "briefly" -- go through some of the results.

One hundred percent of the centers that responded do accept certain donors with a history of cancer, and then former leukemia and lymphoma patients are permanent deferrals at 78 percent of the centers, and a diagnosis of melanoma warrants permanent deferral at 41 percent of the centers.

And by comparison with Dr. Newman's experience, looking at a much larger base of blood donors, beyond that and the carcinoma in situ circumstances, I was really quite surprised as to what sort of variability is entertained amongst the ABC programs.

It was difficult to find exactly what it was that got us into this area of virtually common

agreement, namely, permanent deferral for individuals with a history of leukemia, lymphoma, and melanoma. the earliest reference I could find was an article by John Myelin (phonetic) back in 1977, but his suggestion that those individuals be deferred was not a suggestion that he backed up with any references.

Skin carcinoma, basal and squamous, was acceptable at 93 percent of the centers, and then 77 percent of the centers did accept donors with a history of solid organ carcinoma after a disease free interval of something like five years.

Next slide.

Now, before I say something about the rare circumstances under which tumor transmission has been documented, just a reminder that we really do have no shred of evidence that tumor is transmissible by transfusion.

In fact, when I reviewed the responses top this survey, I was surprised to find the number of occasions that blood center SOPs referred to the importance of the blood center medical director speaking to the blood donor, and it was interesting, the zeal with which the medical director was pursuing the blood donor for documentation of an illness that all of us recognize is not an illness that is

transfusion transmitted.

And in fact, some of the medical directors expressed their exasperation in the role that they have in deciding on the candidacy of the donor with a history of malignancy, exasperation because many of them felt that they were at a loss to appropriately explain to the donor in remission or the donor cured who might previously have had Hodgkin's or a lymphoma, explaining to him or her why he or she was not a candidate to be a blood donor and why he or she if cured should, in fact, be subjected to permanent deferral.

Other items that were of interest in reviewing these responses to the questionnaires I've hinted at earlier, was the broad range of different criteria that are met at the different programs. Some programs found that donors with a history of malignancy, once cured, were acceptable provided they had not been treated by chemotherapy or radiation.

At other centers they were acceptable provided they were ten years disease free, at other centers five years disease free. Other programs permitted individuals with a history of malignancy to donate after a single year of disease free interval.

At other centers no time frame was

stipulated, but the approval of the medical director of the blood program was all that was required.

And some centers said that carcinoma of the cervix, for example, was acceptable provided there was a negative Pap smear. At another center, carcinoma of the breast was a permanent deferral. There certainly did appear to be significant variation in these various centers' approach to handling donors with a history of malignancy.

In spite of the fact that we have no evidence that tumor can be transmitted as a result of blood transfusion, both Dr. Newman and Dr. Simon hinted at some of those rare circumstances, transplantation circumstances where evidence of transmission is possible, and I thought I'd just put up here some of the more recent references:

Glioblastoma being transmitted during the course of liver transplantation;

Kaposi's in renal transplantation;

And then a quite recent report of acute promyelocytic leukemia through liver transplantation.

Both the previous speakers though emphasized the extraordinary rarity of these circumstances, and Dr. Newman spoke about it, too. While we should not, repeat "not," take the experience

in the transplantation setting to be any reflection of what we might consider possible in the transfusion setting, I think all of us have mixed feelings about the outcome of the various discussions of new variant CJD, the stipulations that now apply to donors and deferrals those individuals perceived to be at risk for transmitting new variant CJD.

There really does come a point where we have to have confidence in what evidence there is, and I think this really is an opportunity for us to draw the line. There is no evidence, and we can be confident in the fact that there is none, no evidence that there is a risk for a transfusion recipient should he or she be provided blood by an individual with a history of a malignancy.

What then should we do? My only divergence with Dr. Newman's presentation would have to do with -- we've seen that from Dr. Newman. So I'm going to abandon that as well. Thanks, Joseph.

My only divergence of opinion from Dr. Newman's presentation would have to do with whether we should do studies. I think if we commit ourselves to studies then we're harboring just the hint that maybe there is something there, and I don't think there is even the hint, especially bearing in mind that when we

draw 40,000 donors a day, as has already been suggested, it's highly likely that there is a significant number of individuals who are donating ostensibly healthily, who nonetheless are harboring metastatic perhaps carcinoma of the prostate or even carcinoma of the breast, and there is no evidence in the epidemiology of either of those diseases that receipt of blood for blood transfusion is causative.

And so I think studies would be problematic because it would imply that we do still harbor some concern that there is a cause and effect. One of the other problems with doing studies might be bear in mind the majority of transfusion recipients are the older population, and if we recall Dr. Simon's figures looking for the appearance of a malignancy in an older population which already has a very high instance of malignancy is going to demand studies of such huge size that I don't know how we would really find the funding to support them.

Some individuals have expressed a concern that if there is an infectious etiology for some malignancies, such as Berkett's lymphoma, then should we be concerned about transfusing blood from individuals who do have a history of malignancy. All I would say there is that if, indeed, some malignancies

in addition to, for example, Berkett's, have an infectious etiology, then surely the intravascular route must be an exceptionally inefficient way to transmit that infectious agent. If it were not inefficient, we certainly would have seen the emergency of malignancy as a risk in some transfusion recipients.

So what can we do then? I think here really is an opportunity to be permissive rather than conservative, and in the absence of any evidence for recipient risk, I feel it would be permissible to accept donors with a history of cancer after they have been declared disease free or after they have been released from medical treatment.

Thanks.

MS. CALLAGHAN: Okay. Our next speaker is Dr. Linda Chambers, who is doing this because Dr. Davie couldn't show up. So I'm sure he owes her for this one.

DR. CHAMBERS: Yes. I'll collect, too. Those of you who know me know I don't let anything go by.

I will also limit my comments more to ones of summation at this point because I think you've seen the world's combined literature speaking to the issue of whether cancer is a transfusion transmissible

condition.

I do have copies of my presentation out at the table, too, if they're of interest to anybody, but I'll read the statement just to be sure that I touch, again, on what I think are the salient perspectives and concepts in this arena, and then just share with you how we would like to approach it at the American Red Cross.

I'm currently a senior medical officer for the American Red Cross, and I work at Biomedical Headquarters in Arlington, Virginia, and I appreciate the opportunity to share with you our thoughts on the issue.

Donor health history questions are designed to elicit two kinds of information, that which would indicate that it's unsafe for the person to be a blood donor, and that which would indicate that the blood is unsuitable or unsafe for someone to receive in transfusion.

When you ask a global question like, "Are you feeling well today?" or "have you had a serious illness?" you can elicit responses that are relevant to either or both of those concerns, donor safety or recipient safety, and a history of malignancy is most often elicited from those general questions.

The real crux of the issue is whether a history of malignancy has any implications at all for recipient safety. Does having malignancy per se increase a person's chance of carrying a transfusion transmissible infection? Is there a cancer susceptibility factor that transfers from a donor with a history of malignancy to the blood recipients? And can malignant cells from the donor infuse with the blood, engraft with the recipient and produce a tumor in the recipient?

Well certainly some transfusion transmissible viruses are associated with malignancy. For example, Hepatitis B with hepatocellular carcinoma, NHTLV-1 with T cell lymphoma and leukemia. So for these malignancies, the donor history of cancer may, indeed, identify a donor that has a higher risk of carrying a transfusion transmissible virus.

But donors are screened with serology, and at least for HIV and Hepatitis C now with nucleic acid testing for these agents, and it's unlikely that donor exclusion based on just the history of cancer per se would affect the transfusion risk for the corresponding infection.

Furthermore, it's unlikely that a person with a history with something like hepatocellular

carcinoma or T cell leukemia would ever be considered cured, be healthy, and be presenting as a blood donor.

Is there a cancer susceptibility factor that transfers with blood? Can malignant cells in the blood of the donor end up engrafted and proliferating and causing malignancy in the recipient?

Well, as you've seen, there's no evidence to support, and there's a large amount of experience that refutes that this is a real occurrence. It has been shown that a slurry of malignant cells from a lab animal tumor can engraft in a second animal, but the inoculation material in those experiments is not at all modeled for blood transfusion.

Tumor cells can be found in the blood of patients with extensive and untreated malignancy. Again, you've seen the specific studies that quantitate and look at the viability of those cells, but the engraftment potential of the cells in another person has never been demonstrated, and persons with extensive untreated malignancy, after all, don't present as potential blood donors.

Specific examples, donations from persons with CML contain larger numbers of malignant leukocytes, and these cells are detectable for many weeks to months after transfusion in other patients.

Yet the cells have never been found to engraft, to proliferate, or to cause malignancy in the recipient.

I think it is important in those studies, too, to distinguish persistence of the cells in circulation from engraftment, engraftment being actually the cells finding a spot to take up housekeeping and producing replicates that are then found in circulation in the donor.

There's evidence, in fact, that tumor cells don't engraft even in the patient from whom they came. The studies from interoperative blood salvage are probably the worst case scenario, but think for a minute about autologous collections in patients who have malignancy and are going for curative surgery. In fact, patients who receive autologous blood during cancer surgery have a lower rate of occurrence than comparable patients who receive allogeneic non-autologous blood, despite the potential for those units having contained tumor cells.

But what if malignant cells circulate in peripheral blood in persons who have early small tumors? Could these be viable and transmitted with transfusion?

Well, here we have experience to confirm that this does not occur. Relatively common

malignancies, including prostate cancer, but also colon cancer, lung cancer, and breast cancer, are usually present. They're typically present month to years before first symptoms occur. So persons with occult malignancy are among the ranks of the active blood donors all the time, all the time.

If transfusion recipient were acquiring malignancy from such donors, what we would eventually see is what appeared to be metastatic disease in a patient who had no primary, and in some cases who could not have had the corresponding primary, for example, metastatic prostate cancer in the lungs of a woman.

We would also expect an increased incidence of new and unexplained metastatic tumors without primary tumors in transfusion recipients, and this is not seen.

So the relevance of a history of malignancy is limited to concerns of safety for the donor and the standards for accepting the donor can be written accordingly.

The objective during screening would be to avoid blood donation in a person who had an increased likelihood of needing some sort of serious medical intervention in the near future, like surgery or chemotherapy, and you can deal with this easily by

using standard clinical parameters for when a patient is cured.

Now, for many hematologic malignancies the term "in remission" is preferred to "cured" because the conditions do have a propensity to recur after many years of being quiescent after treatment, and so perhaps for standard leukemia, lymphomas, indefinite deferral is appropriate.

For non-hematologic, solid cancers, all of them are considered cured after the patient has been treated with resection without recurrence or residual disease for something up to five years. Depending on the cancer, it may be as short as immediately after surgery in healing, for example, excision of a carcinoma in situ of the cervix or it could be as long as five years.

We would propose then that that same parameter in the absence of a shorter period defined by an organization, such as the American Cancer Society, to define a cure would be five years without evidence of residual or recurrent disease, and that this be used to determine that blood donation poses no special risk for the donor with a history of malignancy so that all other criteria being met, routine blood donation would be permitted.

Thank you.

MS. CALLAGHAN: Okay. If we could have our last four speakers come up in case there's any questions.

DR. NICKEL: I'm Dr. Jim Nickel from Alpha Therapeutic.

I want to caution you against malignant melanoma. In a yet unpublished paper that I heard about during a pathology meeting within the past month, the question was asked: what's the most people that have ever died from one cancer? And the answer was five.

A young woman, age 41, died suddenly in her shower, and her corneas, kidneys, and I believe her liver also were used for transplantation, and all five people who received the transplants, including the cornea transplants which obviously had very few melanoma cells in them, died within about a year, and they went back and found that the woman had had a biopsy a number of years earlier that, in fact, had been called a mole and was a melanoma and was the source of this melanoma.

So transplantation clearly with regards to melanoma, which has a great propensity to be able to grow in other people, it's a much more malignant, less

differentiated type of tumor than most of our solid cancers. This represents a very dangerous cancer, and I think you saw that 41 percent of the centers defer permanently from melanoma.

I personally believe that that's appropriate, and since you can have these long, long latent periods with melanoma, recurrence is in many cases after a 20 year gap of being, quote, disease free, the five year criterion absolutely does not apply to melanoma.

So I think melanoma represents a special case which we have to be very, very cautious about taking those patients who have ever had a melanoma.

Melanoma in situ, often misdiagnosed as in situ when, in fact, it's really invasive. It depends on how many sections are examined and how thoroughly the work was done initially, and so on and so forth. So even melanoma in situ you have to be very circumspective about accepting a patient who had that.

And did they have adequate excisions? How big an excision has to be done for a melanoma to be cured? We know that you can have satellite lesion and transit metastases, all these other things where the melanoma has actually gotten away from the primary site.

There's now studies being done that help us get a handle on that, like node studies, things like that, sentinel nodes, and we find in many, many of these cases that the melanoma has, in fact, escaped even though there's no clinical evidence for years.

So that's one caution.

There are other cancers obviously that we have to be very circumspect about as well. Hepatoma we heard about just a minute ago. This is a frequent sequela of viral hepatitis, and so I think you're going to find very few of those people who are considered ever to be cured, but if you ever do get one, I think that you shouldn't consider them as cured because they might still have the underlying condition.

Brain cancers of all types obviously have increased risk of seizures if they're operated on surgically.

Breast cancer, there's many kinds of breast cancer. Not every breast cancer is the same. There's lobular cancer and ductal cancer. The lobular cancers have a high incidence of bilaterality. So the fact that somebody has been cured of their lobular cancer in one breast by no means implies that they're out of the woods, that they might not have a cancer in the same breast again or in the other breast.

Many of these cancers are multi-focal also. So I think we need to look at it and realize that there are certain types of cancers that represent much bigger risks than others, especially in transplantation, but I think, you know, obviously no studies have been done on transfusing melanoma patients' blood to other people, and it's a rare tumor. I wouldn't want to be the volunteer who got the blood from a melanoma patient.

So that's my comment, and I'd be interested in hearing what any of the panelists have to say about that.

MS. CALLAGHAN: You're on.

DR. SAYERS: This will be my final answer.

(Laughter.)

DR. SAYERS: You know, we started out disparaging the Australians for good reasons, some of those really disruptable early studies, but there's a country where malignant melanoma has reached proportions which are startling, to say the least.

Is there any evidence in that country that melanoma has ever been transmitted by transfusion? No. Is there any evidence in the world -- and we have three million opportunities a year. That's the size of the transfusion recipient population -- to reveal not

necessarily obviously that melanoma is transmitted by transfusion, but that malignancy is.

You know, those remarks I'm sure are 100 percent germane to organ transplantation. What we're looking at here is blood transfusion, and we've made mistakes before extending our knowledge from one area to another, and given the fact that as we've said, I think, each one of us, that there is no evidence that you can transmit by transfusion, we should be concerned what happens in the transplantation arena, but not extend that to what happens in the transfusion arena.

Conversation?

DR. HOLLAND: No, I want to comment.

This is Paul Holland from Sacramento.

I want to make three quick comments, but I want to respond also to that.

That case actually came from Sacramento. Our organ procurement agency transmitted those tissues. Actually the major problem in that case was that the physician didn't make it clear to the patient and her family that she had a malignant melanoma. She didn't think so, nor did her family, and that's why they agreed to have her organs transplanted. So that was really the issue. Whether she was ever a blood donor I don't know. I don't think so.

I want to make three comments. First of all, one, somebody else said, not me, that absence of risk is not the same as risk of absence.

That having been said, I think we have taken countless donors with cancer that was not evident, and they were healthy at the time, and transfused them without any apparent evidence, known or unknown, in terms of studies to either those donors or to their recipients.

So I would like to enthusiastically support Dr. Simon's approach, which is to take those with a history of cancer, if they're otherwise qualified, meaning they're not under current therapy, and if not, if that isn't acceptable to you all, then his blanket five year rule. I think it's a pretty good rule.

But I would like to take exception for my third point a bit with what Dr. Newman said, and that was the number of donors that we're losing with a history of cancer. I don't know about you, but most centers actively discourage people with a history of cancer from even trying to donate. So we have no idea, and with the numbers that Dr. Simon showed us, there are probably a lot of perfectly good, especially older donors, with a history of cancer who would love to donate blood if they knew it was okay.

I would agree with him on the public relations aspect, but I think if we take a five year rule or some other evidence that they're not currently ill and under therapy, I think would be a pretty safe approach.

We certainly have done it countless of times unknowingly without evidence either from the limited studies we have, but clearly we have transfused a lot of blood from males to females, and as was said, we don't have a single case of prosthetic cancer occurring in a woman. I think that's pretty good evidence.

DR. NEWMAN: Can I make a comment?

I have to agree with you on your comment. It's misleading to just look at deferrals and say that's the story because deferrals look at those people who show up and what happens to them once they show up. It doesn't look at all the people who don't even bother to come in because they have a history of cancer.

We don't know that number.

DR. GROLIN: Grolin, Minnesota.

A comment and a question. The comment is I actually thank and applaud the Armed Services blood program organization under Mike Fitzpatrick, the ASBPO,

which had a wonderful Web site that does a service to all of us medical directors who would love to abrogate our responsibilities for developing myriad lists of things.

And one of the very handy lists that they do provide is a list of medical conditions. In fact, I do use my role as medical director to modify some things for which I think we have evidence to be somewhat less conservative than them, but I think it is a wonderful resource that people should be aware of, and it's something that does help make screening policies somewhat more uniform.

I would like to pick up on a question that Dr. Newman raised in his tremendous variability of reporting or looking back on cancer deferrals, and I guess the question is for Ms. Callaghan.

In light of the fact that error and accident reporting extension to transfusion services will likely increase the number of reports that your place has to deal with about tenfold or more, is it at all clear that we are doing either you, the donors or the nation's safety at all any good by sending the FDA reports of, quote, error and accidents when the donor comes in and tells us that they have cancer now and reported previous donations where at some random point

we assume that the donor had cancer before?

What does the FDA want us to do as far as recording?

MS. CALLAGHAN: That's a good question. I'm not sure. The whole idea, you have -- Larry?

DR. FORREST: At the current time if we get a report of a distribution of a product that was collected from a donor who then tells us that they had cancer, we are classifying that as a recall.

So at this time we want you to submit those reports. Whether we change our mind after this discussion I'm not sure.

DR. SHAPIRO: Shapiro from Chicago.

I want to tell an anecdotal story. We recently submitted to the FDA a new donor eligibility guidelines which we had put in, you know, a better order for our screeners to use. It was alphabetical. We tried to, you know, make sure that there wasn't double references, you know, that we would make it so they'd only refer to one part of the eligibility guidelines, and it was submitted to the FDA for their approval.

It came back with two comments made, that they could not accept, number one our -- we were trying to characterize what constitutes a hepatitis risk,

which is kind of nebulous, but the other part that is relevant to this discussion was how do we handle -- we have a policy of a five year deferral. You know, if the person has been cancer free, no evidence of symptoms for five years, that they're acceptable, and what came back was the FDA reviewer felt that the medical director had to be integrally involved with the assessment of each donor, and that it was not -- that the screeners did not have the medical knowledge to be able to make those assessments.

As a result -- okay. So then I sent back a response to that, but that wasn't -- and basically what was said to us was we can only accept the eligibility guidelines as a package. You know, if you want to continue to dispute this, you can enter any part of it.

So we put it into place. As a result, I've been called probably anywhere from four to five times a day because we put in the policy that they would call me directly. We had been accepting donors for probably the last three or four years with the screeners asking the relevant questions: what was the cancer? What was the treatment? Were you released from your doctor? Do you have any signs and symptoms of recurrence? And if they were all, you know, the correct answers, then the donors were acceptable.

So I've been fielding those calls. In no case have I been called -- you know, the donor will be excused if they have an inappropriate answer. They'll be deferred for the time period or they'll be permanently deferred.

So what I'd like to make a plea for is to understand that if a blood center does put in, you know, very specific instructions for the screeners who are the medical designees at the site, that you know, if we make it specific enough, that they would not ask that the medical director have to be involved in every one of these deferrals.

It's very time consuming, and it hasn't really added to the safety whatsoever.

DR. SIMON: I wonder if that was done because of the way the AABB standard is written, which I know doesn't bear on -- which FDA doesn't have to accept, but probably influences FDA, because it says there that people with cancer should be excluded unless the medical director determines otherwise, and that would imply a case by case rather than making some blanket rule.

DR. SHAPIRO: Well, again, this is a recent phenomenon, and I think this was in light of the understanding by the reviewer that the FDA is now

scrutinizing these policies and wanted to make a statement. I know of no other center or actually I know Jed's center where he does do that, but I know our sister blood bank and other centers where they don't specifically have to be reviewed by the medical director per se; that the policies that exist and the procedure will be acceptable.

DR. NEWMAN: I think you could look at it that way, but in reality, and I've worked at Red Cross and United Blood Services at least, and I don't think any organization that I'm aware of does it on an individual basis. They all have set rules to follow for the nurses or whoever is collecting the blood.

DR. GROLIN: Grolin, Minnesota.

One of the things we're trying to do with standards is to insure that standards come from standards and that other branches of the AABB are not setting standards, as well intentioned as they are.

So, in fact, the permanent deferral for leukemia, five year deferral for solid tumors really falls out of the technical manual, which is a wonderful guide, and for those of us that say, "Okay. Now, what do I do?" it's a wonderful place to turn.

But this, in fact, is clearly an example where a de facto standard has been set by suggestions

that have been created in the technical manual, and interestingly enough in the current edition of the technical manual, it is really much less -- it's written more as an guidance and less of a standard.

DR. SIMON: Can I follow up on that?

I just wanted to follow up on that because one of the things that, you know, Dr. Nickels pointed out to us, that different tumors are different, and one of the things that came out of the presentations, and you've just brought it up, is that many people will permanently defer for leukemia lymphoma, but not for other solid tumors, I guess, like lung cancer or colon cancer where they use five years, and yet two of the greatest successes in cure of cancer have been childhood leukemia and Hodgkin's type lymphoma.

So it seems that some of the practices that are out there somewhat irrational, and I guess this would be a reason to try to do something different than what we're now doing.

DR. CHAMBERS: And if I could pick up on that, too, they're not only irrational, but they're not current, and it seems to me that writing any standard or having an expectation that these kinds of problems be referred to the medical director still begs the question because the medical director then needs some

parameter on which to decide whether the donor is suitable or not.

There is good information, and I think the American Cancer Society is the best source of current perspective with current treatment on the parameters to use to determine that a patient is cured. I mean cured being that they have no higher likelihood of having a cancer diagnosis in the next year than a member of the general public.

And I would think to take their lead on defining when a patient is cured and should be at no particular risk to the donor for donating blood would be a very well founded protocol.

DR. MIETZNER: George Mietzner, Mayo Clinic, Rochester.

I'll preface this by saying I'm new to the whole blood collection realm. I've only been in it for two months. My whole career has been in cardiology. So I'm not real up on the cancer. So that's one of the interesting topics that I have learned quite a bit here today.

My question basically looking back at the time period that a lot of the studies that you all documented, it seems to be the transfusion studies were '45 to '83, whereas the transplantation studies are all

'97 to '99.

I'm wondering why the discrepancies in the dates, and then also tied to that, could that be because of any variances or mutations of cell growth or anything?

And then are we taking the reverse look at this as well? It seems like every study you guys talked about for a transfusion was a proactive study in that we're going to give them the cells. Have we looked back at cancer victims to have they been blood donor recipients?

I guess then a final statement is if one case ever got through, what would that do to our donor pool? It's a PR nightmare.

DR. SIMON: I could just answer the first, and then pass to the others.

The reason that the transmission studies, transfusion transmission studies are old is because they are basically ethically unacceptable by current standards. So the kinds of studies that were done in Australia, I think, could not be done today, and so probably at some point people stopped trying to do those studies.

DR. MIETZNER: Well, I understood that, but like I was saying, can you do it in reverse?

DR. SIMON: Well, that's a large scale epidemiologic kind of study that would be required.

DR. MIETZNER: I know. My medical director always says just because you don't hear it doesn't mean you look for it either.

DR. CHAMBERS: But you would find, and I think you can trust, that the unusual cancers -- think of what the model would be if it were transfusion transmitted. You'd be presented with a patient with apparent metastatic cancer with an unknown primary of a morphology and a source that could not be possible in that patient.

So you would eventually see something that was impossible if it were a transfusion transmissible condition.

The number of cases where there are metastatic tumors without primary, I mean, they're not rare. They do occur, but with the current availability of things like immunohistochemistry, it's pretty easy to nail the tissue source of malignancy. So adenocarcinomas are relatively easy to subdivide and determine the primary.

I can trust that prostate cancer with a typical morphology in the lung of a woman wouldn't go undiagnosed and unnoticed or ovarian cancer in a man

probably wouldn't be slotted as simply an adenocarcinoma of unknown primary because it has a specific enough morphology that it would cross someone's mind that it would look at ovarian, and then with immunohistochemistry and other current techniques for slotting the tissue source of that malignancy, they would eventually stumble on what appeared to be a very unusual occurrence.

You know, I think we just have a lot of experience. I think we can feel very confident that those wouldn't have gone unnoticed.

I understand your point. The fact that you haven't heard about it doesn't mean it isn't happening, but surely, you know, apparent metastatic prostate cancer in a ten year old child would be a case report in somebody's journal someplace, and it has not occurred, and it's predictable that somebody would have given the sorts of cancers that occur occultly in blood donors all the time if it were a real phenomenon.

DR. NEWMAN: I think if we had a documented case, I think we would have to change our thinking. That's really what would be -- it only would require one case to really relook at this whole philosophy.

DR. NICKEL: The problem that you have is the type of cancers that might be transmitted in

transfusions would be your very undifferentiated or stem cell types of cancers, melanomas, and very undifferentiated cancers, and it wouldn't be obvious that it came from a male or female. It wouldn't be like a prostate cancer among women or breast cancer in a man or something like that. It would probably be a very, very undifferentiated cancer that would be transmitted.

And I don't know personally of any studies that have been done, immunohistochemical or cytogenetic, that have looked at this, but you're absolutely right that this would be one way you could look at it, to take all those people who have metastatic carcinomas or metastatic tumors in which there's no evident primary; look back and see how many of them got transfusions; then go back and look at those donors and see if any of them had that type of tumor; and then you could match them cytogenetically and immunohistochemically and see if there was any incidence of that type of transmission.

That sort of study would not be that expensive to do also, I think.

DR. BIANCO: Celso Bianco, New York Blood Center.

Let's not forget that we are not looking at

the slides or the pathology or the x-rays. We are looking at medical history. What is the likelihood that biomedical history by saying somebody that had a breast cancer that was treated a few years ago and the person is okay, that that person would have such an undifferentiated tumor?

So a medical history, actually we have all of these questions about donor suitability and medical history, and we should remind ourselves we have absolutely no idea of the sensitivity and specificity of the questions that we ask. We do not know how much they contribute to blood safety, and I think that we have plenty to hear today indicating that questions about cancer do not contribute to receiving safety.

DR. HOLLAND: Paul Holland, Sacramento.

I wanted to actually respond partly to what Dr. Nickels said. I believe Dr. Paul Tarter a number of years ago did a study in which he looked at transfusion recipients to see if they had an increased frequency of cancer, and he did it because he theorized, along with the discussion tomorrow, that the leukocytes in the cells increase the risk of cancer and cancer recurrence.

And what he found when he matched them with controls in the hospital, he found that patients who

had been transfused had, in fact, half the frequency of cancer of patients who had not been transfused when matched by age, sex, and a number of other variables.

Now, he interpreted that to mean it was the opposite of his thesis that transfusions did not cause cancer or make people more susceptible to cancer. You could also interpret it to say that there was no evidence of transmission of cancer because those who didn't get transfused had twice the frequency of cancer.

MS. SALAH: Rose Marie Salah from the Intergen Company now in Milford, Massachusetts.

I have just a comment that I would like to say that I'm very happy that you're starting to look at some potential donors who have in situ cancer, that they may possibly be reentered into the blood donor program.

It's a little different. I'm sitting here as a cancer survivor, and I was a victim of breast cancer in situ, ductile carcinoma in situ, and it was very distressing to me when after five years I tried to donate for my mother-in-law who was dying and was told that I was deferred. I was very surprised because I had never had chemo. I had never had radiation. I had just had surgery, and I found it after talking with the

medical director I would never want to do anything that would jeopardize a recipient, but I also felt that I wanted to donate if it could help somebody.

And I was surprised that the consensus from the medical director was, "We just don't accept anybody who's ever had cancer because we are so ambivalent with all of these regulations that we don't know who we can take and who we can't take. So anybody who's had a history of cancer of any sort, of any kind, they're just being eliminated from the donor pool."

I find that distressing because you now have donors that maybe are perfectly safe for the recipient who could be donating, and they're not able to, and that's very disheartening because obviously then as I related my story, a lot of people said, "Well, gee, I had this. That means I can never donate either."

The bad public relations you may not be aware of it, but I was so upset that I found out that I could never donate. I mean, I thought it was like, okay, do I have to wait another five years and then I can donate. No, you can never donate. That is so disheartening for somebody who really wants to donate, not because you ever want to transmit a disease, but because you want to help.

And you've got a whole segment of the population that will never be able to donate because the perception is they can't. So if you are going to make exceptions, you need to get that publicly noted, and you need to inform your medical directors because there's so much ambivalence that medical directors do not want to have to take the onus on themselves to make that decision. So in order somewhat to protect themselves, they just blanket say, "No, we won't accept anybody."

And I'd just like to hear what some of your responses are to that.

DR. CHAMBERS: I think you speak to the point made earlier that we don't know how many people never appear as a potential blood donor because they've heard through the grapevine that they're ineligible with a history of cancer.

I think part of the harm done globally, too, is that the patient dealing with the resected, cured cancer is getting a mixed message. They're safe and they're cured and they fine as far as their physician is concerned, but they're ineligible as a blood donor for some reason. I mean that's a mixed message in terms of their health and their potential for cancer in the future that doesn't do anybody a

service.

MS. SALAH: Well, having come from a health care background myself, I knew that I would never be able to donate for at least five years. So when I came to now donate, it had been five years, and I was very surprised: no chemo., no radiation, just excision. Why?

I mean I couldn't understand it scientifically why, and that's part of what my question is. Do we really need to revisit this a little bit more? Are you excluding too many potential donors without any risk to a recipient?

DR. SIMON: I think the answer to that most of us would probably say is, yes, we are, and that's I assume why the FDA --

MS. SALAH: I'm sorry, but I was devastated when they said no.

DR. SIMON: But I think that's why the FDA presumably is having these workshops, is to relook and to see particularly with the availability issues that face us whether we can begin to reform some of these and get people back in.

DR. SHAPIRO: You made a very good point because this is something that I ran into. Somehow or another empirically we decided that carcinoma in situ

of the uterine cervix was okay. As a trained anatomic and clinical pathologist, I know that cancer in situ is an entity that, you know, you see in a lot of tumors, and as we have better detection methods we are catching tumors earlier and at in situ phases.

Now, it can be a sampling problem, but for the most part when somebody had cancer surgery, they're staged, they have -- you know, their prognosis and their treatment is dependent on the veracity of, you know, this stage of the cancer, whether it's in situ, whether it's invasive, to what level it's evasive, you know, that there's nodal spread.

So I'd also like to say that there should be some understanding that cancer in situ or carcinoma in situ in any organ is not the same as invasive cancer, and so that should be also part of the decision making when we decide whether or not somebody has cancer.

And I've tried very hard to educate my center. Somebody that has carcinoma in situ does not have cancer that's invasive cancer in the traditional sense, and people disagree with me because of the, you know, empiric uterine cancer in situ.

DR. SAYERS: I think your experience with being deferred as a donor is really emblematic of how

we have managed to set the stage for blood donors to be confronted with information which they perceive to be contradictory to their own sense of good health, and any opportunity that we can find to remove those contradictions, be they your experience or be they nonspecificity in screening tests, we should really look for that opportunity to restore the donor's faith in the donation process.

DR. NICKEL; I agree totally with what you all have just said with regard to these cancers that are only semi-cancers, totally curable. The patients have five years of being disease free. We're doing these people a terrible disservice by not letting them donate, and I think that it's definitely the time now, and this conference is obviously trying to do this, to address and break out those cancer conditions in which we should treat those people differently and accept them now as donors once we're sure they're cured, and to sort of keep in mind that there may be some which are more dangerous and which they shouldn't accept just because, quote, they had cancer without knowing more about the type of cancer.

So I hope that all of our in situ cervical cancers and breast cancers, and you can even have in situ carcinoma of the lung, that these patients --

there will be a mechanism in the near future for us being able to take them.

DR. SHAPIRO: What about working with the Cancer Society? Why don't we, you know, kind of hold hands with our colleagues there?

DR. CHAMBERS: I think it's a great idea. I mean they've got as part of their charter to understand the natural history of different cancers in terms of current treatment, and that's what we don't keep -- you know, we can't keep current with what the recurrence rate when you get this kind of intervention versus that kind of intervention is.

But they certainly in their practice parameters need to define a point at which certain cancers can be considered cured, cured meaning you tell the patient, "You're okay. Go to the mall. Have a nice day and you don't have to come back every six months. We're not going to put you through, you know, special screening over and above what we would do for the general population, and don't worry about it."

So they define those points as a function of the cancer, and in some cases along with the treatment, but what you could do is use whatever the longest period is of no evidence of recurrence or disease that would constitute a clinical cure in their

world and say, "Where are we going to have a better cue as to when a person should be allowed to be a regular blood donor?"

You know, if you have any residual concerns about whether cancer is transmissible by transfusion, it's a little harder, I think, to deal with it that way, but if you see it strictly as a donor safety issue, you don't want to collect blood from someone who may in a short period be diagnosed with the recurrence of cancer and go in for treatment. Then this concept of cure is a very powerful concept. It defines the endpoint for you, and it would be different for Hodgkin's disease than for CML, and it would be different for CML than it is for childhood leukemias.

But they are all defined parameters by organizations that know a whole lot better than we do what the natural history of these diseases is.

DR. SIMON: Doesn't it get real complex like for breast cancer? You have receptor positive and negative, and you have X number of nodes?

DR. CHAMBERS: You do. You do.

DR. SIMON: And would we be better off having something which says when the treating physicians has released the individual, indicated that they're cancer free and considered cured, that we could

accept them?

DR. CHAMBERS: I think usually five years is the longest point of disease free.

DR. SIMON: Yeah.

DR. CHAMBERS: So you can just default to whatever the longest period is for all the variabilities. Take out all of the details, the subcategories, and just ask what is the longest period. What is the worst case scenario? And apply that. That's where the five years comes from as far as I know.

The last time I checked five years was the outer limit on any of the solid tumors, but certainly for other select ones that occur with some frequency, like childhood leukemias and Hodgkin's disease, it's a shorter period than the five years, and I think taking their lead on what that shorter period might be appropriately would be that wouldn't be valid.

DR. SIMON: As guidance to the physicians who might be called to evaluate it.

DR. CHAMBERS: Exactly, exactly.

MS. SALAH: May I just bring up one more point? Prior to my getting breast cancer, I was terrified to donate blood, terrified, and as were many other women that I had encountered in the same type of

a situation.

Having survived and having had successful surgery, there's an onus of wanting to give back, and now you have many people who never wanted to donate now who do because there's a sense of gratitude and wanting to help somebody else.

So if we're a safe donor, please don't exclude us because there are so many people who are so grateful and to now be told you're deferred forever is devastating, and you're losing a whole bunch of potential donors.

As long as we're safe and as long as we would never hurt anybody, please don't exclude that in situ type cancer victim.

Thank you.

DR. MIETZNER: George Mietzner from Mayo again.

Off the cancer issue I'd also like to put in some support for the hematocrit/hemoglobin issue because in my short two months in my office I have already fielded five calls from ladies that have left our facility being told they were deferred for low hemoglobin and immediately called their physician and made an appointment and had their hemoglobin checked with their physician.

And I know that I agree because it's on the low end of normal, I'm working as a training issue with my employees to do that, teach them that it's not your hemoglobin that's low. It's just our acceptance criteria.

But so if we could alter that at all, I think it goes back to we're telling somebody that believes they're fully healthy that there's a problem with their hemoglobin.

MS. CALLAGHAN: Okay. I'd like to thank all our speakers. We had some very interesting discussions, and it has given us a lot of food for thought as we go on to try to revise the donor suitability criteria. Thank you, everybody, and thank you for attending.

(Whereupon, at 4:40 p.m., the workshop was concluded.)