UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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PUBLIC HEALTH SERVICE

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION & RESEARCH

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BLOOD DONOR SUITABILITY WORKSHOP

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MONDAY, NOVEMBER 23, 1998

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The workshop took place in Conference Rooms D and E, Parklawn Building, 5600 Fishers Lane, Rockville, Maryland, at 8:30 a.m., Andrew Dayton, M.D., Ph.D., Chairman, presiding.

PRESENT:

ANDREW DAYTON, M.D., Ph.D.	Chairman
CELSO BIANCO, M.D.	Speaker
MICHAEL P. BUSCH, M.D., Ph.D.	Speaker
KEN CLARK, M.D.	Speaker
LYNDA DOLL, Ph.D.	Speaker
SIMONE GLYNN, M.D., MPH	Speaker
HAROLD JAFFE, M.D.	Speaker
BERNARD POIESZ, M.D.	Speaker
SUE PRESTON, Ph.D.	Speaker
TOBY SIMON, M.D.	Speaker
RICHARD STEKETEE, M.D., MPH	Speaker
SUSAN STRAMER, Ph.D.	Speaker

PRESENT (cont'd):

GEORGE SCHREIBER, D.Sc.	Speaker
ALAN WILLIAMS, Ph.D.	Speaker
IAN WILLIAMS, Ph.D.	Speaker
THOMAS ZUCK, M.D., FRCP (Edin)	Speaker

ALSO PRESENT:

DAVID FEIGAL, M.D.

A-G-E-N-D-A

A-G-E-N-D-A (cont'd)

P-R-O-C-E-E-D-I-N-G-S

(8:40 a.m.)

DR. FEIGAL: Good morning. Maybe we could get started. I'd like to welcome you to FDA's Workshop on Blood Donor Suitability.

I'm David Feigal. I'm the Deputy Medical Director at the Center for Biologics.

And one of the more important responsibilities -- one of the responsibilities actually recognized in the last revision of the Public Health Service Act in 1944 is our responsibility for assuring the quality and the safety of the blood supply.

Today's workshop is intended to gather scientific information to assist the FDA and the Department of Health and Human Services in efforts to update and revise blood regulations on donor suitability.

It has only been about two decades since we began explicitly asking donors to self-identify or began looking at the kinds of factors that might be risk factors for transmitting infectious diseases.

And since that time, much has changed, both in our knowledge of the epidemiology, in the emergence of infections that we were unable to even

test for two decades ago, and in our knowledge of the transmission.

The way that the process works is that regulations are promulgated in the Code of Federal Regulations. Fans of the CFR know these as, in the book of numbers, as Sections 21 CFR 610 and 640.

And when we propose a change in regulations, the process which we go through to do that is to first carefully, and in consultation with advisory committees and with workshops and with our partners in the public health service, including the Center for Disease Control and the National Institutes of Health, develop the scientific basis for updating the regulations.

Today is part of that process for taking a look at these specific regulations. Another part of the process which moves more quickly than changing the regulations is to use guidance documents.

These, in the past, have had various names -- Points to Consider, Blood Memorandum -- although we unified all of the ways that we deliver guidance through a procedure we call Good Guidance Procedures. And so now all of these different vehicles are called guidances. And we are able,

through this process, to actually also communicate important information.

Several of the exclusionary criteria we're discussing today were initially issued as guidance documents. And one of the questions, as we go through the updating process, is since many things that come out that are done initially are done through guidance and they don't have the binding force of a regulation, when is it appropriate to turn the guidance into regulation so that that standard is enforceable, since the regulations are our interpretation of the Public Health Service Act and sometimes the Food, Drug and Cosmetic Act?

More broadly, I guess, today we're looking at the very first parts of the multiple layers in the safety net of the blood supply. This step that we're looking at today first begins with providing educational material, screening donors by asking the donors questions about their health and risk factors.

This means that trained personnel need to be able to interview the donors and help determine if that's a suitable donor, and find out if potential donors should exclude themselves.

The FDA recommendations and regulations to exclude potentially infective donors have expanded over the years as we've sought to exclude for risk factors for hepatitis B and HIV, but also included such viral variants as -- and looked for the donor exclusion questions that would also identify high risk for HIV Group O and the thorny issue of the theoretical risks for diseases such as Creuzfeldt-Jakob disease.

The second part, after donation, is that blood is tested for blood-borne agents, including HIV, HBV, hepatitis C and HTLV I and II. This, in fact, gives us feedback in terms of how successful we are in some of the donor exclusions and provides some of the scientific basis for identifying our success in this process.

The difficulty and the reason why testing cannot completely replace donor exclusion is because of the difficult issue of window periods -- that time when someone is infectious but you cannot yet detect it with your blood screening tests.

Today we'll hear scientific information on the risk of transmission of HIV, hepatitis B, hepatitis C, the HTLVs, and emerging infectious diseases, in categories that have been identified for exclusion in the past -- men who have had sex

with another man even one time since 1977, men or women who have exchanged sex for money or drugs since 1977, and men or women who have abused intravenous drugs. We will also hear presentations on the risk to partners of such individuals.

The underlying question that we're grappling with in looking at our current guidance and regulations is whether the FDA should maintain the lifetime exclusion for these individuals that have been described as being involved in these activities.

And also at issue is the rationale of deferring sexual partners for such persons for only 12 months.

We will begin and hear the epidemiology on the introduction of retroviruses into human populations. We'll hear information on the incidence and prevalence of HIV, hepatitis, and HTLV in individuals who engage in activities thought to be at high risk for infection.

We will hear a presentation on the prevalence and incidence of blood and plasma donors and the impact of the donor deferral criteria on blood safety. And we will consider the advances in donor testing and narrowing the window period by the

introduction of investigational genetic tests for HCV and HIV.

We'll also consider a model to assess the impact of changes for these donors.

The challenge before us is to maintain safety and availability of blood plasma and products and balance the enthusiasm, based on improvements gained by advances in test technologies, with due caution based on the past unfortunate experiences of being unable to stop disease transmission with the methods of those days.

I'd like to just conclude by welcoming you all. I think that it's a testimony to how interesting and important this topic is that we have such a good turn out and such broad representation at this time of year during a holiday week.

And let me introduce Dr. Andy Dayton, who will also make some introductory remarks.

DR. DAYTON: Good morning. Thank you all for being here, and welcome to the Donor Suitability Workshop.

I think you've had a very good introduction as to what our scientific questions are today, and all I'm going to do is just remind all of us of the theoretical framework in which the FDA tends to look at deferral issues.

This is what we're trying to prevent, obviously, infection getting from potential donors into the blood supply. Our main weapon for this is, of course, tests for infectious agents.

Could I have the next overhead, Martin?

Okay. So we have tests to prevent bad things from getting into the blood supply. But tests are imperfect, and here are ways that infections get into the blood supply, bypassing tests. We essentially have prevalence issues.

In this case, it would be undetectable strains of a pathogen which the current tests don't recognize. In this general category would also, of course, come emerging pathogens which have not -- for which there aren't good tests -- blood bank errors -- these are very rare. And general failure rate of the test depends on the test. Certainly, for something like HIV, this is essentially zero.

And then we have incidence issues by which infectious agents can bypass the tests, and this is the window period that Dr. Feigal referred to.

Martin, can you move that up a little bit now?

So that we can actually -- in an ideal world, we can actually calculate the total number of

infectious slipups, total number of times we get an infected unit slipping into the blood supply.

And it merely equals the number of blood donors times the prevalence times the summation of these various errors for the prevalence issues. And for incidence issues, it's blood donors times essentially an incidence factor, which is described here.

Can I have the next overhead? Okay. That's good.

Now, how do we -- is this perfect? Well, no, this isn't perfect. Things can get around the questionnaire as well as getting around the tests. If society is well educated, we have a large number of self-deferrals, which is good.

The questionnaire which we have designed to block the people from -- infected people from actually becoming potential donors can also be bypassed not only by self-deferral, but there are ways in which the questionnaire can fail.

And these are very difficult issues to pin down. For instance, ineffective risk identification. If we have not appropriately identified a certain risk category, those people will, of course, get through the questionnaire and get to the testing stage.

Test-seeking behavior -- you see this in people who show up to the blood donation centers because they know they're going to be tested. And even if they know they're in a high-risk category and they're not supposed to show up, they appear because they know they can get a test.

Sometimes there is resentment. And it's a very easy thing to understand how people can feel resentful towards being told that they're not appropriate for giving blood.

Peer pressure -- a group of people all decide to give blood at, let's say, some kind of community organization, like a church, and peer pressure can induce people to give inaccurate answers on the questionnaire.

Misunderstanding of questions. If it's a poorly designed questionnaire and somebody doesn't understand what's being asked, you can have people inappropriately getting through the questionnaire.

And this is a -- we're not going to discuss the questionnaire issues very much today, but it's a very significant problem, because the questionnaire is getting fairly long and there's a lot of interest in subcategories in high-risk behavior, to see if we can factor out lower-risk subcategories of what we currently consider high-

risk behavior. And that can give you a problem in making a very complicated questionnaire.

Could I have the next overhead, Martin?

So how do we approach this? Well, there are two ways. I really should say prospective approach, or forward approach, for the first way of doing it. And that's to determine all of the numbers that feed into that model that I just showed you, and we will be discussing that data today.

We want to know the prevalence, the incidence, and how that factors out according to risk behavior. We want to know the size of the behavior categories, and that's important in determining the number of blood donors that we have from that category.

We would like to know blood bank error rate. We don't have a lot of good data on that. We would like to be able, of course, to quantitate undetected strains. Easier said than done. We would certainly like to know accurately the assay failure rate for other reasons, and I think we probably have reasonable data on this in most cases.

And we really want to know what is the behavior of the various risk groups in terms of self-deferral and questionnaire behavior. And this is actually a very complicated question and a very

major question because -- and it will be addressed today in several talks.

But when you don't know how many people in a certain risk category are going to correctly answer the questionnaire, or how many are going to self-defer, it makes it very difficult to estimate what the risks are of having that particular behavior group donating blood.

Could I have the next overhead?

And then there's the retrospective approach in which we look at failures and determine their sources. And we'll see data on this today, too. The typical example of this would be to take case histories of post-transfusion episodes. Now, this is particularly important for emerging pathogens in early stages of epidemics when there aren't good tests.

More relevant to what we're doing today is identifying and categorizing the risks associated with the units that test positive. You can consider this basically as a reality test for the calculations that we would have made with the data I just -- the kind of data I just indicated we look for. Or you can consider it as the truest assessment of direct threats to the blood supply --

in other words, residual risk. This is what the blood testing centers and the tests actually see.

The next overhead, please, Martin.

Now, I'm not going to dwell at this on length, but in certain special cases pertaining to changes in policy, which is often what we're faced with, sometimes a modified approach can be pursued to calculate the effects of policy changes. For those of you who, about a year ago, came to the MSM presentation of the BPAC about a year ago, this is what we approached that issue with.

If a deferral policy is already considered adequately safe, and that's a big if -- but if it is considered adequately safe and there is perhaps a desire to change the policy, for example, from a highly restrictive policy such as lifetime deferral to perhaps a less restrictive policy such as a one-year deferral, one can ignore the bypassing of the questionnaire issues, which, as I said, is a very difficult thing to calculate.

And the reason you can do this is because anybody who's already bypassing the questionnaire would be unaffected by the enlarged inclusion categories -- in other words, the narrowed exclusion categories.

Or another way of saying that is they're already getting to the testing stage under the current policy, and they'll still get through the questionnaire after the new policy, whether they intend to be newly included or not.

So in situations like this, one can then assess the effects of changes in policy simply by appropriately multiplying the prevalence and incidence rates in those first equations I showed you by the expected donation rates in a high-risk behavior category, and the size of the newly-included category, to estimate new challenges to the testing step. And I won't dwell on this further.

Let me just sum up in the last -- so there are many different aspects of a transfusion-transmitted disease that must be understood in order to understand its risk to the blood supply and to appropriately formulate a policy deferral -- or deferral policies.

There are different approaches to estimating risks, and they're often complementary and are rarely mutually exclusive. We seldom have all the numbers we need to perfectly estimate risk. It's not a perfect world.

Because of these indeterminacies, we must build redundancy into the system. And you can

see that, and that's basically why we have both test and questionnaires.

We must always consider -- and here I haven't discussed this at all, but it will be the subject of our first talk. We must always consider the great unknown of emerging, poorly understood, poorly characterized pathogens, because we can't pick them up with the questionnaires always and we can't pick them up with the tests always.

And we feel -- the FDA feels very strongly that the public and Congress have made it clear that they desire a zero error tolerance policy with respect to the blood supply. In other words, the health of the recipient of the blood or the blood products must always be our primary concern.

So with this very brief overview, I want to thank you for your attention.

And let me introduce our first speaker, Harold Jaffe, who will talk on the introduction of retroviruses into human populations, a model for emerging pathogens.

DR. JAFFE: Good morning. I'd like to thank Dr. Dayton and the FDA for inviting me to be with you.

While I'm not entirely sure how my topic is going to relate to the rest of the meeting, I was

very pleased to see the term "emerging pathogens" used because it makes my bosses at CDC smile.

What I'm going to try to do is examine the epidemiology of retroviruses that are known to infect humans as a model for emerging blood-borne pathogens. And while, clearly, HIV 1 is the most important and well understood of these, I want to compare and contrast HIV 1 with some of its retroviral relatives.

Could somebody turn the first slide on?

Okay. Well these are the subfamilies of the retroviruses that we're concerned about, and they include, of course, the lentiviruses.

Now I can't see. I don't need to see, do I?

The lentiviruses, HIV 1 and 2, and their simian counterpart -- SIV -- which, as I'll point out, has actually infected humans; the oncoviruses, HTLV I and II; and the spumaviruses, which are also known as foamy viruses.

For each of these subfamilies, we can really ask the same questions. We can ask: where did the virus come from? When was it introduced into humans? Once it was introduced, did it spread? If it did spread, what were its transmission routes?

And once it spread, did it establish itself in any particular populations?

Then, based on the answers to these questions, I want to see if we can draw any general conclusions about the likely epidemiology of a new blood-borne agent.

Let's just start with some very basic information that I'm sure you mostly know about HIV 1.

As I'll illustrate in a moment, the closest relative of HIV 1 among the non-human primates is the chimpanzee simian immunodeficiency virus, SIVcpz. As I'll also try to illustrate in a moment, although we don't know exactly when HIV 1 first occurred in humans, it was probably on the order of about 50 years ago, although the global spread clearly didn't occur until later than that.

We all know that it causes AIDS, and we all know its basic routes of transmission. A major question for this meeting, of course, is: which group should be considered at highest risk for these various infections?

For purposes of AIDS and HIV surveillance in the United States, these are the categories that CDC considers to be exposure groups for HIV 1 and, of course, they include homo and

bisexual men, injecting drug users, persons with hemophilia, transfusion recipients, and the group reporting specific heterosexual contact with an HIV infected person, or someone known to be at increased risk for HIV.

Now I want to look at some of these points in a little bit more detail, the first question being: where did HIV 1 come from?

And how does this thing work?

Okay. This is a phylogenetic tree, which you probably can't see. And if you could see it, you probably wouldn't be able to figure it out. But I'll try to point out some of the important points.

This is a tree that was published just a few months ago by Simon & Associates. And what it does is compare the genetic sequences in the envelope region of HIV 1 and the chimpanzee lentiviruses. You can disregard this part down here which deals with HIV 2.

The point it makes is that, first of all, we can see three groups of HIV 1 viruses -- the Group M, O, and N. Group M is, of course, the major group. It's the one that's responsible for the global pandemic. And it includes a number of

subgroups lettered A to J, some of which are shown here.

This appearance is called a star phylogeny by the people who work in this area. And what they say is the star phylogeny suggests a single introduction of an ancestral virus that then evolved into these many subtypes.

Now, of course, Group M is the predominant subgroup of HIV 1 in the world, and it's the one that's really responsible for the global pandemic, but there are several other groups as well. The Group O viruses, which are shown over here, were first reported in 1990.

They're genetically quite distinct from the Group M viruses. They're found mainly in Cameroon and adjacent countries in Africa, although two African patients have been reported with Group O infections in the United States.

Finally, in the article that I just mentioned by Simon, the authors describe a new subgroup, Group N, which is represented by a single isolate again obtained in Cameroon from a person with an AIDS-like illness. And this is thought to be a prototype for this new group.

There are also two chimpanzee viruses shown up here, CPZant and CPZgab, which represent

viruses from Zaire and Gabon, respectively. The genetic distances on this tree are indicated by the branch lengths. And you can see that the Group M and the Group O viruses are not particularly close to these chimpanzee viruses. But the Group N actually is quite close to this virus from a chimpanzee in Gabon, and it appears likely that these two are highly related.

I think most people in this field believe that there were separate introductions of ancestral viruses, most likely from chimpanzees, that resulted in these three groups of HIV 1.

Now, if it's true that each of these HIV 1 groups has its own ancestor, when were these ancestors introduced into human populations?

The only group that we really have much information for is the Group M, the predominant virus in the world. And this comes from a study that was done by David Ho & Associates in which they were able to look at a plasma sample that had been collected in 1959 from what was then known as the Belgian Congo and were able to obtain at least a fragmentary genetic sequence of a virus in that sample.

It's shown here in yellow. And the point is that this sequence seems to be very close

to the hypothetical ancestral strain from which the subtypes D, B, and F viruses were derived.

Based on what's known about the evolutionary rate of HIV 1, these authors suggest that the Group M viruses probably shared a common ancestor, perhaps in the 1940s or the early 1950s.

Now what happened after these viruses were introduced into the human population isn't really known. I think most likely the viruses did spread relatively slowly in parts of sub-Saharan Africa for a number of years, and it's possible that the spread then accelerated with the social disruption and population movements that occurred following the end of colonial rule in many of these countries in the 1960s. In retrospect, there probably were clinical cases of AIDS in some African cities by the mid 1970s.

How and when the virus entered the United States is also not known. In collaborative studies that CDC conducted in San Francisco, we found that, looking at serum samples that had been collected from gay male STD patients in 1978, about five percent were seropositive.

It would be nice if we had comparable data from injecting drug users and other groups at that time. Unfortunately, we don't. One way we

might gain some insight, though, into the very early spread of HIV in the United States and the resulting AIDS cases is simply to look at this chronology of the first reported AIDS diagnosis in these various exposure groups.

This is based on CDC's surveillance data. I've excluded a couple of very early cases that seem pretty questionable. But it's interesting to see that, in retrospect, the first case of what we now call AIDS that was diagnosed in a gay man actually was in 1977, which was four years before the epidemic was recognized.

Two years later, we had the first case in an infant born to an at-risk mother and in a transfusion recipient; in 1980, the first case in an injecting drug user; and, in 1981, the first case in a hemophilic and in a heterosexual contact.

Again, I wouldn't take this chronology too literally, but I think it would at least give us some idea, or a rough idea, of how the virus was spreading in the early years in the United States.

The story of HIV 2, I think, bears many similarities to HIV 1, but there are some important differences that I want to try to emphasize. Like HIV 1, we think that HIV 2 as derived from a non-human primate -- in this case, the simian

immunodeficiency viruses that affect sooty mangabeys.

We don't know when this crossover happened. The first documented infections, in retrospect, in humans were in specimens collected in West Africa in the 1960s, but the virus certainly could have been there before then.

The geographic distribution of HIV 2 -- we know that it's by far the most common in West African countries and in several of the former Portuguese colonies in Angola and in Mozambique, but certainly has not had the same kind of worldwide spread that we've seen for HIV 1.

We know that HIV 2 causes AIDS, but the rate of disease progression is certainly lower than what we see for HIV 1. And while the roots are the same, as I'll point out in a moment, the rates of HIV transmission by these routes are substantially lower.

Within the United States, the only group that can be considered to be at increased risk for HIV 1, at least right now, would be persons born in certain West African countries.

Now, trying to look at these points in a little bit more detail -- again, this is a phylogenetic tree, which is certainly confusing.

But it's also kind of interesting, and I'll just try to point out the main points it's trying to make.

This comes from Beatrice Hahn & Associates, and it looks at a series of subtypes of HIV 2 virus, AID F, shown here. The HIV 2 strains are all shown in white. And simian strains, particularly from sooty mangabeys, are all shown here in yellow.

The important point here is the genetic relationship between the human virus HIV 2 and the simian viruses is very, very close. It's much closer than what I showed you previously for HIV 1 and the chimpanzee viruses. In fact, the relationship is so close that we can use HIV 2 antibody tests to detect these simian infections.

Beatrice Hahn has suggested that each of the HIV 2 subtypes that are shown on this slide probably represent a separate introduction of an ancestral SIV strain into a human population.

The differences in the rates of HIV 2 transmission compared to HIV 1 are really very striking. This slide, for example, looks at the rates of perinatal transmission of the two viruses in three studies, two of them from West Africa and one in France.

You can see, as you would expect, the HIV 1 transmission rates, in instances where the mother has not been treated, between about 20 and 25 percent; but, for HIV 2, between about zero and one percent.

We can also see differences in the sexual transmission of HIV 2 versus HIV 1 in this slide which comes from a study done by my colleague, Kevin DeCock, while he was working in Abidjan in Côte D'Ivoire.

This study looks at the infection rates of HIV 1 and 2 in childbearing women. You can see, for HIV 1, in the blue bars, that over the period observed -- I think from 1988 to '92 -- HIV 2 seroprevalence increased from about five percent to about nine to ten percent. But during that same time, the HIV 2 prevalence actually decreased from about two and a half to one and a half percent. So in the same populations, the two viruses are actually behaving rather differently.

The reason for the lower transmission rate of HIV 2 is not entirely clear, but Kevin DeCock has suggested that a major factor explaining this might be the lower concentrations of virus found in the blood of HIV 2 infected people, especially during the early phases of infection.

This slide examines virus isolation rate from peripheral blood mononuclear cells stratified by CD4 count. You can see for HIV 1 high rates of virus isolation from anywhere from high to low CD4 counts, but that's not the case with HIV 2.

In the relatively immunocompetent HIV 2 infected patient, the virus isolation rate is quite low. It would be nice to be able to confirm these findings with plasma HIV 2 measurements, but reagents for these tests are just now being developed.

The lower transmission rate of HIV 2 I think can help us understand why the sexual spread of HIV 2 has been much more limited than HIV 1. The spread of any infection can be described by a term which is called the "basic reproductive rate," or BRR, of an infectious disease, which is simply the average number of secondary cases generated by a primary case.

If this rate falls below one, an epidemic cannot be sustained. For a sexually transmitted infection, BRR depends on three factors: the rate of partner change, the duration of infectiousness, and the transmissibility of the agent.

So even if HIV 2 infected persons have just as many sex partners as an HIV 1 infected person, and even if they remain infectious for their lives, the lower transmissibility of HIV 2 will limit its spread.

I think we get a good example by looking at the CDC surveillance data for HIV 2 infections in the United States through June of 1988, at which point we knew of 79 HIV 2 infected people in this country. Of these, 52 were persons known to be born in West Africa. There were another 15 whose birthplace was unknown, but four of these had malaria serology profiles, suggesting a West African residence.

So unlike HIV 1, there has not been a major HIV 2 epidemic in this country. And groups identified to be at increased risk for HIV 1 have not necessarily been at increased risk for HIV 2.

Finally, before leaving the subject of HIV 2 entirely, I just want to mention a case report by Rema Khabbaz and her associates at CDC of SIVhu, "hu" standing for human infection. The index case here that was published a couple of years ago was a laboratory worker who handled clinical specimens from SIV infected macaques.

The worker was found to be seropositive using HIV 2 antibody tests, but sequencing the virus infecting this worker revealed that the virus was actually an SIV which appeared to be highly related to the virus of sooty mangabeys that was being studied in this laboratory.

To date, this worker has not become ill, and the worker's steady sexual partner is not infected. This occupationally acquired infection may, therefore, be a contemporary model for what happened in the past when sooty mangabey viruses were introduced into humans, and subsequently adapted and evolved into what we now recognize as HIV 2.

Let's now shift to the second subfamily, the oncoviruses, and begin with HTLV I. Like the viruses that we've already described, it, too, has a relative among the viruses of non-human primates -- in this, case STLV I -- which is widely distributed among these animals.

Unlike HIV 1, it's believed that HTLV I entered the human population many thousands of years ago, and since then spread to most parts of the world. And, of course, unlike the lentiviruses, these viruses do not cause immunodeficiency diseases; rather, cause a

malignancy -- adult T-cell leukemia, lymphoma, and a neurologic disease known as HIV 1 associated myelopathy or tropical spastic paraparesis. Again, the same transmission route -- sexual, parenteral, and perinatal. But, as I'll point out, the transmission rates are certainly lower than what we've described for HIV 1.

The highest prevalences of HTLV I in this country are seen in persons born in Japan and in the Caribbean and in injecting drug users, although most HTLV infections in injecting drug users in this country turn out to be HTLV II.

As I just mentioned, HTLV I is clearly less transmissible than HIV, and one can see that from a number of studies. Some of them I've tried to summarize for you here.

For example, in looking at children born to infected mothers in the absence of breast-feeding, we see the transmission rate again for HIV 1 above 20 percent, and about five percent for HTLV I; for transfused blood, about 90 percent for HIV 1; and a number of studies for HTLV I, rates between 13 and 64 percent, which seem to depend on the concentration of lymphocytes in different blood products and the storage conditions.

The importance of the very strong cell association of HTLV I is seen even more dramatically when we look at studies of recipients of non-viral inactivated clotting factor concentrates.

In a study that was done in 1988 of about 200 U.S. hemophilic patients, we can see that almost 80 percent of them were infected with HIV 1, which, of course, is present both in plasma and in infected cells, versus zero percent for HTLV I, reflecting the lack of infectious virus in the source plasma used to manufacture these clotting factors.

While the studies that have been done in the endemic parts of the world, particularly the Caribbean and Japan, do demonstrate the sexual transmission of HTLV I, again, the transmission rates are considerably lower than what we know about for HIV 1.

For example, U.S. studies of HTLV I have shown a striking lack of infection in homosexual men. The example shown here was a study done in the late 1980s by investigators from the National Cancer Institute looking at HTLV I infection rates in homosexual men in major U.S. cities in which HIV 1 infection rates were very high.

But yet, for HTLV I, we see the virtual absence of infection -- one out of 1,200 in Los Angeles; zero out of 300 in these other parts of the United States.

Now, why this is the case is not entirely clear. Perhaps there's been relatively little interaction between these men and others at high risk for infection such as injecting drug users. But thinking back to our discussion of the basic reproductive rate, it may be that the lower transmissibility of HTLV I through sexual contact has not allowed an epidemic to be generated in this particular population group.

Whatever the reason, the important point is that groups at increased risk for one retroviral infection are not necessarily at risk for all retroviral infections, despite the similar transmission routes.

HTLV II has been studied less extensively, but also appears to have derived from a simian virus, STLV II. Again, it was thought to have been introduced into humans thousands of years ago, and it's found mainly in this part of the world in Indian tribes for both North and South America. It has also been reported to be endemic in certain pygmy tribes in Central Africa.

Although the virus was first isolated from a patient with hairy cell leukemia, the disease associations in humans are not well established. Similar transmission routes, as we've talked about before, in the highest prevalence in the United States for HTLV II in injecting drug users and some North American Indian tribes.

Finally, I just want to mention something that you may not have heard so much about, a more recent infection introduced into humans, and that is simian foamy virus infections in human populations. These viruses are known to be quite common in a wide variety of non-human primates, but there really is not good evidence for an endemic human foamy virus.

The virus infections in humans that we know about are largely the result of cases in which workers have been occupationally exposed through their work with non-human primates, their viruses, or other laboratory specimens.

This slide summarizes a CDC study in which about 230 persons who worked with non-human primates were tested for antibody to foamy virus. And four, or about two percent, were found to be seropositive. Subsequent genetic sequence analysis showed that one of these workers was infected with a

foamy virus from an African green monkey, and three others with baboon viruses.

All of these workers appear to be well. And the three spouses that were studied, all of them are seronegative. It's tempting to speculate that these represent dead-end infections. That is, infections that, although they were transmitted from primates to humans, will not be transmitted from one human to another.

However, we know one of these individuals did donate blood, and we know of a more recent case who was also a regular blood donor, and we're hoping to initiate look-back investigations of their recipients.

To try to conclude, then, let's look at some of the lessons that might be learned by examining the introduction and the spread, or lack of spread, of retroviral infections into humans. First of all, these infections appear to have originated in non-human primates. Second, cross species transmission of the oncoviruses probably occurred thousands of years ago, while the lentiviruses were introduced much more recently.

The nature of the contact between human and non-human primates that resulted in these transmissions is not known, but the contemporary

examples illustrate how occupational exposure has introduced SIV and foamy virus infection into humans.

Third, once these viruses were introduced into the human population, even though they spread through the same routes, their rates of transmission are substantially different, probably related to biologic differences in the virus, such as the degree to which they're cell associated and their ability to grow or not grow to high concentrations in human tissues, which presumably reflects how well they've adapted to the human host.

And finally, looking in the United States, so-called risk groups for these infections vary considerably depending on the virus that we're talking about, and not all risk groups are the same.

Presumably, the spread of viruses into these groups resulted from some combination of factors, including the geographic and temporal proximity of these groups to the source of the virus, the interaction between persons in these groups and other infected people, and risk behaviors in these groups.

Now, what I've told you about these retroviruses may or may not apply to other emerging blood-borne infections, but I think there is one

lesson that does apply overall, which is, it's a jungle and we need to be careful out there.

(Laughter.)

And I want to thank my son for downloading that from the Internet.

(Applause.)

DR. DAYTON: At this point, we'd be very happy to welcome questions on any of the talks so far. If anybody has any questions or comments, please raise a hand, go to a microphone.

Jay?

DR. EPSTEIN: Harold, I think you raised the most intriguing question, which is that risk groups for one infection may not be risk groups for another infection. And I wonder if you could turn it around and just comment on what one can do as opposed to what one can't do.

Are there commonalities that we should worry about -- for example, STDs?

DR. JAFFE: Well, if we look at all the viruses that we do know about, all the retroviruses -- I mean, one common theme clearly is blood exposure -- that both the oncoviruses and lentiviruses have established themselves who are exposed to blood, for example, by needle sharing.

For sexual transmission, I don't actually see that the link has been made. I don't know who's talking about HTLV I, but, as far as I can tell from what I reviewed, HTLV I has really not established itself, for example, in gay men in the United States, which I find quite odd since it is sexually transmitted in endemic areas.

It has certainly been around a long time. There certainly is some interaction between injecting drug users and gay men, and yet we just don't see that gay men in this country have increased prevalence of HTLV I.

At least I'm not -- if that's wrong, I'd like to be corrected.

MR. DODD: Thanks. Roger Dodd from the Red Cross.

Actually, Jay, my favorite example is an infection which may or may not be transmissible by transfusion, but it's human granulocytic Ehrlichosis. And in The New England Journal, in a particular study, the greatest risk group that was identified for being infected with this agent was having a lousy golf score because people went into the woods to collect their balls.

This didn't apply to women who were too smart to go chasing after lost balls.

(Laughter.)

But I raise the point because it speaks directly to the issue that you raised, Jay, that we don't necessarily have to use retrovirus as a model for all future potentially transfusion transmissible agents. And I know that muddies the water, but I think it's an interesting point.

DR. RUTA: Hi. Martin Ruta, FDA.

Dr. Jaffe, I was wondering if you could describe some of the surveillance mechanisms that exist within PHS and our ability to detect either variants or emerging agents that might pose potential threats to the blood supply.

DR. JAFFE: I can at least describe some of the things that we're doing at CDC. I can't speak for the rest of the PHS. I guess the simplest thing we do, and it has actually been fairly productive, is that when clinicians are aware of oddball cases -- people who appear to have AIDS or an AIDS-like illness and have either "funny serologies" or are seronegative -- we often get calls and we often receive those samples. So we do have a chance to look at them.

We also do look at persons reported with AIDS who were born in Africa and residing in this country, just thinking that so many of the subtypes

are present in Africa that, if something unusual were to pop up, maybe we would find it that way.

We have more formal surveillance going on in a number of countries overseas, again emphasizing Africa, where we're trying to use testing algorithms that are not necessarily subtype specific.

For example, we've used more generic techniques -- for example, the AMP RT method -- to look at persons with AIDS-like illnesses who test negative using conventional serologies but with a test that would detect really any retrovirus.

So we do have a number of systems in place. At the same time, I would be the last one to believe that that system is foolproof and that, if new viruses were introduced into this country and were not causing obvious disease, or were not causing it for a number of years, I don't think we have a system in place that would find it.

DR. BIANCO: Celso Bianco, New York Blood Center.

Harold, what is very interesting in your presentation is that you showed that the variants that you see in retroviruses, in general, are less virulent or less transmissible than the predominant forms. Make you almost suspect that, by selection,

that the most virulent are the ones that are succeeding in the pandemic.

But is it applicable -- should we assume that, because we were using before always the model of the resistant bacterium, that in a certain way we would not have the means here to diagnose there to treat with antibiotic?

Is that the model that we should use? That is, that the variant will be the most virulent, or the least virulent, or you can't make --

DR. JAFFE: I think it would be hard to generalize. I mean, clearly, among the retroviruses that are established in humans, HIV 1 is the most virulent and probably was the most recently introduced.

So, you could look at that and say, well, that's the one that maybe is the least well adapted to humans, or the human host has not been able to develop an immune response that's protective.

On the other hand, the foamy viruses that we know about that have just been -- presumably have not been introduced into humans in the past -- at least we have no evidence for it -- in the small number of people who have been studied, don't seem to cause any disease at all.

So again, I think it would be hard to generalize.

DR. DAYTON: Okay. If there are no more questions, let's proceed to the next speaker.

We're now going to have a talk from Ian Williams on prevalence and incidence of HBV and HCV in various high-risk groups.

DR. IAN WILLIAMS: Thank you very much.

There's a lot more people here than I expected. I brought some handouts, but they're definitely not going to go all the way to the back. So I guess I'll start in the front, and we'll run out about a third of the way back.

It's my pleasure to be here this morning. I probably have one of the more difficult talks to give this morning due to, really, the paucity of data. So I'm going to do what I can to present the data that's out there and suggest limitations, where appropriate, and hazard some guesses where I think those are also appropriate.

I thought it would be important, to sort of put this all in context, to start from the general and work to the specific. What do we know about the general U.S. population in terms of hepatitis B?

And actually, this is a very nice study that's going to be published this January in the American Journal of Public Health by Geri McQuillan and her colleagues at the National Center for Health Statistics, in conjunction with the folks at CDC.

And basically, this data comes from the Third National Health and Nutrition Survey. And essentially, this is a population-based cluster sample that seeks to make estimates about a number of health and nutrition outcomes for the entire U.S. population as a whole.

And I'll get right to the bottom line. What did they find? The bottom line is they found that roughly five percent of the general U.S. population has ever been infected with hepatitis B. And when they broke it down and looked at its certain population subgroups -- and again, this is a study that's not set up to look specifically at blood-borne pathogens, but to look at other health and nutrition outcomes.

When they looked at it and stratified it by the ways they were able to, they basically found that rates of hepatitis B virus infection varied quite a bit depending on what population subgroup you looked at. If you looked among non-Hispanic

whites, they found rates of about two and a half percent.

If you look among non-Hispanic blacks, you saw rates of about 12 percent. And if you looked among Mexican-Americans, you saw rates of about four and a half percent. So there's quite a bit of variability based on who you look at.

And on this slide, I don't present data on those that are chronically infected, but if you look -- and the numbers start to get pretty small -- overall, the rates of chronic infection are about four-tenths of a percent.

That translates into about one million Americans. So roughly 12 million Americans out there are infected with hepatitis B -- have ever been infected, and about one million are chronically infected.

So what do we know about the incidence of hepatitis B as a whole? Well, basically, the incidence has been declining in recent years. Back in the mid to late '80s, we think the incidence peaked at roughly around 300,000 new cases per year. But since then, there's been a tremendous decline in the number of cases, and we think we're now down to in the ball park of 150,000 to 200,000 new cases.

So in the last 10 to 15 years, the incidence of disease has been half, and this is due to a number of different factors.

We noticed a tremendous decline among homosexual men and health care workers beginning in the mid to late '80s. Some of that is due to changes in risk factor behavior, as well as introduction of a very good, very safe, effective vaccine back here in the early 1980s, although it took a number of years to percolate into those groups at highest risk.

And since the vaccines being out there and people have been getting the message about, namely, HIV, we reap the benefits of HIV education because hepatitis B is spread in many of the same ways. So we also saw a decline, basically, predominantly among injecting drug users starting in the mid '90s.

Whether that's actually due to those prevention messages getting out there, we're not clear. But regardless, the incidence is dropping -- has dropped quite dramatically in the United States over the past decade.

So what are the risk factors for hepatitis B in the general U.S. population? And

basically, they hit all the risk groups I'm going to talk about here later this morning.

Basically, roughly half of acute hepatitis B over the last decade is due to a sexual route. That is, either a heterosexual, which accounts for about 35 percent of everything, 39 percent, and homosexual transmission, which accounts for roughly 13 percent.

This data actually comes from our sentinel county surveillance study which has been done in four counties dating back to 1982. And essentially, what we do is we look at acute cases of viral hepatitis of all types and interview them and draw sera, and actually, for some subselected groups, follow them over a period of time.

So this is a very good way for us to track emerging infections. And actually, hepatitis C, which I'll talk about in a minute, was actually discovered in the serum that gave rise to -- some of the antibody tests actually came from the sentinel county -- was a case of non-A/non-B hepatitis.

But regardless, this study basically interviews people who are acutely ill and then they admit to risk factors. This will become more important when we talk about hepatitis C. But basically, there's a group of people who admit to a

whole, broad range of risk factors who actually don't admit to traditional risk factors such as a heterosexual partner or having a homosexual partner.

And basically, we think that all of these other people down here are essentially those that are a little truth challenged, as one of our nurses say. A lot of these people probably have all these other risk factors up here, but basically aren't admitting to them on interview.

So we think roughly in the ball park of maybe up to 50 to 60 percent of hepatitis B is sexually transmitted, and maybe up to 15 to 20 percent is through injection drug use.

Okay. So let's talk a little bit about the specific risk groups we're interested in this morning.

I thought I would present this data in the following fashion. It's important not to, when we talk about these risk factors for the population at large, talk about what is the prevalence of these characteristics in the population at large.

Basically, even though there's quite a bit of variability, when you look in the general population and look through the literature, you basically find that in the ball park of between one-half and five percent of the U.S. population has

ever used injecting drugs. And this is quite a big range and really depends on who you ask and what studies you look at.

I think most people think it tends to be towards the lower end of this range than the upper end of the range. But in the published literature you see ranges of between one-half and five percent.

If you look among men who have had sex with men, this may represent up to ten percent of the general population. I could find no good data on how many people have ever been a commercial sex worker. I'm sure that data exists someplace; I just couldn't dredge it out of the literature.

There's no data on how many infected sex partners of hepatitis B are out there, or hepatitis C, but there is some good data that looks at lifetime sex partners. Again, this comes from the National Health and Nutrition Survey.

And basically, you find that roughly 20 percent of the U.S. population has had only zero or one lifetime sex partner. Fifty percent of people had between two and nine lifetime sex partners. Twenty percent have had between 10 and 49. And four percent of the U.S. population has more than 50 lifetime sex partners.

So even though we don't have a prevalence for commercial sex workers, some would think that, if you had more than 50 lifetime partners, you're probably a commercial sex worker or likely to be a commercial sex worker. So this number is probably much less than four percent, to hazard a guess.

So let's talk about the specific risk groups one by one. Let's talk about with injection drug use. Basically, hepatitis B is found in very high prevalence among injecting drug users. Roughly 60, 80 percent of people who have used injection drugs have hepatitis B.

What do we know about hepatitis B in these populations? Well, the seroprevalence varies quite a bit by age. It's strongly associated with age. The older you are, the more likely you are to become infected. And this is actually shown very clearly in the National Health and Nutrition Survey.

However, you do see some variation in prevalence by geographic region and risk factors within the injecting population. That is, different injectors use different drugs, some snort, some shoot, some shoot in different ways. So you have to think about when you look at prevalence of hepatitis

B exactly what's going on in the population you're studying.

However, risk seems to increase quite dramatically with number of years of drug use. And if you look at people who have injected within at least five years, you find upwards of 90 percent of people who have injected at least five are infected with hepatitis B.

It's tough to come up with measures of incidence because injecting drug users are a very difficult group of people to follow, to get them to come back. But the ball park sort of estimate out there is probably around four percent per year of injectors become infected with hepatitis B.

However, these studies always need to be interpreted with a grain of caution because not only is hepatitis B spread through injection, but it's also spread through a sexual route. So you need to be very careful to separate out sex from the drugs when you look at these studies, and not all studies are very careful to do that. So you have to interpret the incidence figures with some caution.

Well, speaking of sex, what do we know about the prevalence of hepatitis B in various sexual characteristics. Well, as I mentioned earlier, hepatitis B seems to be spread fairly

efficiently through sex. If you look among men who have had sex with men, you see seroprevalences of 20 to 40 percent. And basically, you find about the same seroprevalences among commercial sex workers, in the ball park of 10 to 40 percent. And these are also the same you see among STD clinic patients.

If you look among infected partners, you see seroprevalences of about 40 percent as well. You also see an increasing prevalence, based on number of lifetime sex partners, which peaks out about 12 percent among those who have had more than 50 lifetime sex partners.

So I hope you're convinced now that hepatitis B is transmitted fairly efficiently through sex. STDs play an important role in the transmission of hepatitis B, we believe. When you look at people with hepatitis B, at least 40 percent of these people have had an STD previously. And whether this is a marker for high-risk sexual behavior or may facilitate transmission was a little up in the air, but at least 40 percent of people have had a previous STD. Men who have had sex with men are at an extremely high risk of hepatitis B.

Risk factors include those of other sexual transmitted diseases, including multiple

partners, receptive anal intercourse, and history of other STDs as well.

It is very difficult to get estimates of incidence for hepatitis B among men who have sex with men today. But if you look back in the pre-vaccine era -- this is, again, sort of the pre-HIV era as well, back in the late '70s and early '80s, you see incidences up to 13 percent per year. I think we feel that the incidence is tremendously lower than that, basically due to use of hepatitis B vaccine in this population and exchanges in risk behavior.

However, it's important to remember that the seroprevalence among men who have sex with men, as well as these other risk groups, varies quite a bit by age, geographic region, risk factors, and, since there's a good vaccine, vaccine coverage within these populations.

Okay. So let's move on and talk about hepatitis C. This is, again, data from the National Health and Nutrition Survey, and this is the source of the oft-quoted number that roughly 1.8 percent of the general U.S. population is infected with hepatitis C or has antibodies for hepatitis C. And this translates into roughly four million Americans.

When you look at this data again, you find that it varies quite a bit by population subgroups. You find that roughly one and a half percent of non-Hispanic whites are infected with hepatitis C, roughly 3.2 percent of non-Hispanic blacks, and two percent of Mexican-Americans.

And actually, an interesting finding with this data is this is a cross-sectional study. That is, you take people at one time, over a short period of time in many different ages. If you take this data and actually plot it out by the age of the person interviewed versus how many are anti-HCV positive, you see a very interesting shaped curve.

You basically note that there is a big hump among the sort of middle-age groups here. And it reflects the increasing prevalence that we saw among the different population groups in the previous slide. That is, intensity lower among whites, somewhat higher among Mexican-Americans, and highest among blacks.

And if you bear with me for a second, I just drew some arbitrary lines here on this graph, and basically selected those between 30 and 50 years of age. And basically, if you look among those 30 to 50, and average the proportion that each of these groups accounts for in the general U.S. population,

you basically find rates of about three and a half percent among those 30-to 50-year olds, and much lower rates among those older than 50.

This also gives rise to a number of interesting hypotheses that are often quoted in the literature -- that the seroprevalence is much higher among to 30- to 50-year olds. We may be on the edge of an epidemic of chronic liver disease in this country. That is, as these cohorts start to age and move this way, we may be starting to see more and more chronic liver disease caused by hepatitis C. But that's the topic of another talk.

So let's talk a little bit about incidence. The prevalence is extremely high -- roughly two percent of the U.S. population. The incidence seems to have declined quite dramatically over the last decade or so. Basically, back in sort of the mid to late '80s, we think we saw in the ball park of about 150- to 200,000 new cases every year in the United States.

Basically, since then, due to a number of issues I'm not going to really talk about today, we saw a tremendous decline among transfusion recipients, starting in the mid '80s. And basically, that sort of started some of this decline. But we've also noticed a tremendous

decline among injecting drug users in the last decade or so. And why this is happening is a little unclear, but it may have to do with saturation of the population at large, which I'll talk about here in a slide or two.

So what are risk factors for hepatitis C in the United States? Again, this is data from our sentinel county study, which basically interviews patients with acute hepatitis C and seeks to find the risk factor. The bottom line is: injection drug use today is the number one leading source of hepatitis C in the United States.

It's pretty remarkable to me that 40 percent of people will admit to using injecting drugs within the last six months upon interview. Roughly 16 percent of people admit to either having more than two sex partners in the last six months or have sex or are having sex with a person who we believe they know is anti-HCV positive.

If you'll look at this piece of the pie, roughly two-thirds of these people have an anti-HCV positive sex partner. Two of them have had more than two sex partners in the last six months and deny all of these other percutaneous exposures.

Again, since these people are interviewed and some of them tend to be a little

truth challenged, when you look at people who really report none of these exposures here, basically you find they have a whole broad range of other risk factors. We think that probably another 14 percent of this pie, or accounting for about 60 percent of the total, are drug related. That is, these people are probably failing to admit to injection drug use that are actually injecting.

And we think that some of these people with a history of STD may be denying multiple sex partners. So we think that roughly about 60 percent of acute hepatitis C in the U.S. is due to injection or illegal drug use, predominantly injection, and roughly about 20 percent is due to sexual transmission.

This is a little controversial, as we'll talk about later on. However, we don't have any data on concurrent STDs in these people, which may explain why we see a higher rate of sexual transmission in this study than other people have seen. But I'll talk about that at the end.

An important point for this group is that only four percent of people report a transfusion or transfusion-associated. And interestingly, if you look at the data -- we've seen

no transfusion-associated cases since 19 -- there have been no cases in 1995 and 1996.

And actually, we've only seen one case since 1992 when better screening became available. So this four percent is somewhat misleading because it's heavily weighted towards the 1991 end of this spectrum. So transfusion association cases seem to be declining quite dramatically in the U.S.

Okay. So let's talk about injection drug use. I've told you that injection drug use is the number one leading risk factor, and it also shows up in the prevalence data. Roughly 50 to 90 percent of people who use injection drugs are infected with hepatitis C.

Again, caveats apply. The seroprevalence tend to vary quite a bit by age, geographic region, and risk factors in the injecting population. And that explains that somewhat big spread between 50 and 90 percent. So it depends on who you look at, where you look at, and what the injectors are actually doing in that population.

However, we do know that the risk increases quite strongly based on the number of years injecting drug use. And we find that basically upwards of 90 percent of injectors are

infected within one to two years of the time they start injecting.

And depending on the studies you're reading, again, these have to be taken with a note of caution. You see incidences of up to 10 to 20 percent per year. That's right -- 10 to 20 percent per year.

However, there is some caveat that needs to be thrown in. A lot of these studies were actually done back in the late '80s and early '90s. There has been some studies today that seem to suggest that this incidence may actually be declining quite a bit. And why that is happening is a little unclear and may have to do with needle exchange programs, messages about HIV prevention that are getting out to the new injectors out there.

It's a topic that needs studied a little bit more. But regardless, the incidence rates tend to be tremendously high. And a lot of people have trouble buying into that the incidences are really actually that high.

And this actually is a very good study that was done by the folks in Baltimore, the ALIVE study, and what they basically did is looked at a group of injectors and asked them, "How long have

you been injecting?" And then tested them for HIV, hepatitis B, and hepatitis C.

And here is what they found. Everybody thinks about HIV and injectors, and roughly 20 percent of the people were infected with HIV, but that came in number three in terms of blood-borne pathogens. HBV came in number two, with roughly 40 percent of people, by the time they started injecting, infected with hepatitis B. And this tended to increase very steady over the next two years. And actually, if you follow these people out for six years or so, it tends to plateau. So right around 60 to 70 percent.

But if you look among those with hepatitis C, basically 50 percent of people, by the time they got enrolled in a study, already had hepatitis C. And it very quickly went to 80 percent, within basically the first six months of the time they started injecting. And then it slowly worked its way up to 90 percent. And if you follow these people over the next five or six years, it sort of peaks out around 90 percent or so.

So basically, hepatitis C is acquired very, very rapidly through injection drug use, which makes it very difficult to do prevention strategy, since, again, roughly everybody is infected by the

time they started injecting or very quickly have become injecting.

One other thing it's important to appreciate is is that the incidence of hepatitis C varies quite a bit, depending on when you're looking and who you're looking at. And these are the four primary sentinel counties we look at. And, again, this is our surveillance system that looks at acute cases of all types of viral hepatitis.

And just to give you a feel for where these are, Pinellas County is Tampa/St. Pete, Jefferson County is Birmingham, this is the city/county of Denver, and this is Tacoma, which is about 40 miles south of Seattle.

And basically, what do you see? Basically, you can see from this graph -- and again, these are on the same scale -- that the incidence varies quite a bit depending on where you look. And it also indicates that you could have very large outbreaks of hepatitis C among injectors in the community. We saw a tremendous outbreak here sort of through the late '80s and early '90s among injectors in Pierce County.

So you have to sort of look at these data -- look at incidence data with a little bit of -- a grain of salt, I guess.

So let's talk about hepatitis C and sex. Basically, when you look at men who have sex with men, it doesn't seem to be nearly as high as you would expect. Basically, the seroprevalences of around four percent are out there. I didn't present a range for this because the range is a little misleading. Depending on what study you look at, you see ranges from one percent to 15 percent.

The 15 percent is only in one study and seems to be a little bit of an outlier, but I'll talk about more of that in a second. But overall, I think the feeling is you see seroprevalence of around four percent among men who have sex with men.

You see seroprevalences, again, between one and 20 percent among commercial sex workers, although it tends to be more towards the lower range than the upper range in the majority of studies. Among infected sex partners, you see seroprevalences of roughly one and a half percent, although there needs to be a lot more work to look at this group. But that's probably a reasonable estimate.

You also see that the seroprevalence increases by number of lifetime sex partners, with those who have more than 50 lifetime sex partners have seroprevalences approaching 10 percent.

Again, this should be taken with a grain of salt as well, because this comes from the National Health and Nutrition survey, which didn't ask about injection drug use. So basically, we don't have any idea how many of these people actually acquired it through sex and how many got it through injection use.

And it's probably a reasonable assumption that people who have more than 50 lifetime sex partners -- at least some proportion of these people are participating in injection drug use activities. So the seroprevalence is probably much lower than is actually presented in these slides once you take out history of injection drug use.

So let's talk about sex. This is one of the more controversial areas of hepatitis C research now, and it's an area that needs a lot of work. Basically, the overall opinion is the efficiency of transmission of HCV through sex is relatively low. What does that actually mean? Well, it basically means transmission can occur, transmission is probably rare between long-term steady sex partners at least, although the actual risk of transmission is unknown.

We're in the process of trying to set up a study to look at this. The general feeling is

it's probably going to be less than one percent per year, which, again, makes studies very difficult to do because the incidence is relatively low. But nobody is really ready to hazard a guess among infected sex partners, among long-term steady sex partners at this point, other than to say that the incidence seems to be relatively low.

However, on the other hand, when you look at hepatitis C as a traditional sexually transmitted disease, basically you find it more frequently among people with high-risk sexual behaviors. And the risk factors, when studies have looked at it, seem to be -- for hepatitis C infections, seem to be pretty much the same you see for other STDs. That is, multiple partners, histories of STD, and failure to use a condom seem to be associated with HCV infection. So it sort of looks like it could be a sexually transmitted disease.

However, when you look among men who have sex with men, they have about the same risk as basically -- as heterosexuals do for this. So it seems to be a little confounding. And why this is true is unclear, and it's, again, an area for future research. But it seems to sort of fly in the face

of reason that it seems to appear to act like an STD, but it doesn't appear to act like an STD.

However, one of the major limitations of a lot of these studies is they haven't really looked at other risk factors associated with transmission. There may be other factors that may promote transmission of HCV in a sexual arena, such as viral titer and other concurrent STDs. Again, it's unknown whether other alterative STDs may facilitate HCV transmission, and this is an area of important research.

Another important thing is that a lot of these studies, especially done among commercial sex workers and STD clinics, failed to do a good job of separating sex from injection. We know that hepatitis C is very, very efficiently spread through injection drug use. And if you don't do a good job of teasing out those that are injectors from those that have a pure sexual route, you can very easily contaminate your data and get to wrong results.

And finally, although there is sort of developing data on this, again, the seroprevalence for HCV seems to vary a little bit or seems to vary by age, geographic region, as well as risk factors in the population -- namely, injection drug use and sexual activity.

So if you have to summarize everything onto one slide, which I tried to do here, basically, you find that hepatitis B is a relatively -- occurs in about five percent in the U.S. population, is spread relatively efficiently through sex, and spread very efficiently through injection drug use. Hepatitis C occurs in about two percent of the population, is probably spread less efficiently through sex, but very, very efficiently through injection drug use.

Thank you very much.

(Applause.)

DR. DAYTON: Thank you very much for that excellent talk. We'll have an opportunity to discuss this and the other talks in a panel discussion coming up.

The next talk will be from Rick Steketee on prevalence and incidence of HIV in high-risk groups.

DR. STEKETEE: Thanks very much, and I, too, would like to thank the organizers for inviting me.

I was asked to speak on HIV prevalence and incidence in certain groups who engage in high-risk behaviors.

Specifically, I'll show some data from a variety of CDC-supported studies among men who have sex with men, or MSM; among injection drug users, or IDUs; and among women who report exchanging sex for money or drugs. I've limited it to women not because men don't exchange sex for money or drugs, but because our studies have a tendency to be more clear on that particular risk group.

The data I'll show come from a variety of sources. These include anonymous unlinked seroprevalence surveys that sampled consecutive persons attending selected STD clinics or drug treatment centers. In addition, in some STD clinics, persons who accepted counseling and testing for HIV on two or more visits were examined for incidence in the interval.

Data was also drawn from the national counseling and testing system database, and from young men's surveys, which are venue-based surveys from street outreach clubs or bars in young gay men.

All risk behavior categorization is based on self-reported or participant here. And for simplicity of categorization for the presentation, we limited the analysis, as I mentioned, just to women who are exchanging sex for money or drugs, and

we'll be referring to them as commercial sex workers.

Finally, as usual, the data comes from the work of many people at state and local health departments, and some community-based projects, and investigators at CDC. And I'm pleased to present the information for them.

Let me begin with data from counseling and testing system in 1996, which is our last year of complete data collection and analysis. This slide shows the seroprevalence in various groups. Remember that they're from an amalgamation of persons who accept or seek HIV counseling and testing at publicly-funded sites, including anonymous test sites, STD sites, drug treatment centers, family planning clinics, adolescent clinics, etcetera.

There were approximately 2.5 million tests done in these settings in 1996, and the HIV prevalence was highest in MSM reporting injection drug use -- around 9.5 percent -- and next highest in MSM not reporting injection drug use, around 6.6 percent. And it was 4.5 percent in heterosexual injection drug users and lowest, 1.2 percent, in heterosexuals not reporting either MSM or IDU.

This map shows data from anonymous unlinked serosurveys and HIV prevalence in MSM attending STD clinics in 14 cities in 1997. Note that the bar scale is from zero to 40 percent, which is generally -- and the HIV prevalence is generally high in this population of MSM and STD clinics, ranges from 3.6 percent in Seattle to about 36 percent in Atlanta. The overall median prevalence for MSM in STD clinics was 20 percent.

This map shows comparable data on women attending STD clinics, and note that the bar scale has changed from zero to seven percent, instead of zero to 40 percent. Again, prevalence is fairly consistent across the country, but ranges from approximately one percent in Denver to about five percent in Miami.

And this map shows HIV prevalence in injection drug users attending drug treatment centers in 12 cities in 1997. The scale is back again from zero to 40 percent. And as has been seen in the past, there is high prevalence generally in the east and substantially lower prevalence in the west, where prevalence overall, the median prevalence in injection drug users was 15 percent for men, and for women it was 11.6 percent.

This slide shows HIV prevalence in women who reported exchanging sex for money or drugs, or commercial sex workers, in three different settings. HIV prevalence was 9.7 percent in commercial sex workers attending drug treatment centers, 6.1 percent in those attending STD clinics, and 3.5 percent of those reporting commercial sex and attending various counseling and testing sites.

Next what I'd like to do is show some data on HIV prevalence among those reporting the risk behavior during the past year, compared to those reporting the risk behavior more than a year ago and not during the past year.

Among attendees at an STD clinic in 1997, this shows reported risk in yellow -- I'm sorry, reported recent risk in yellow and past risk in blue, among men who have sex with men, among heterosexual IDUs, and among commercial sex workers.

Although HIV prevalence varied a little between the groups, and across recent versus past risk behavior, all groups have reasonably high HIV prevalence.

This slide shows similar data from drug treatment centers where HIV prevalence was high and did not differ by recent or past reported risk

behavior in injection drug users or in commercial sex workers.

Finally, I'd like to show a few slides on estimates of HIV incidence in these risk populations. While prevalence is indicative of cumulative acquisition of infection, incidence tells us about recent or current transmission patterns. This slide shows incidence per hundred person years in MSM, in women and heterosexual men in STD clinics repeatedly tested during 1991 to 1996, in seven different U.S. cities.

The measured incidence varied from seven per hundred person years in MSM in Houston to very low rates in heterosexuals in Denver. That is, around one to two per thousand person years, as opposed to seven per hundred person years.

And this slide shows HIV incidence in STD clinics with heterosexuals in yellow and men who have sex with men in red. Of interest, incidence in MSM gradually declines with increasing age, and amongst heterosexuals it gradually increases slightly with increasing age.

However, in those less than 40 years old, the incidence of HIV in MSM is between three and 10 times higher than it is in heterosexuals.

Finally, with the assistance of the San Francisco Health Department, we were able to obtain incidence estimates in one population -- that is, men who have sex with men -- in one city in various venues in a recent year. As you can see, first of all, that the incidence over here, total in the STD clinic, is about one per hundred person years. In MSM, in that environment, it's about four-fold higher.

And in two other types of venues -- that is, anonymous testing sites and out in venue-based surveys -- the incidence of HIV roughly varies between two and four per hundred person years. And it is not greatly dissimilar across the different sites.

So in summary, in 1997, HIV prevalence and incidence is still high in traditional risk groups. Among men who have sex with men, this is true in a fairly wide geographic distribution, in a wide age range, across various venues of surveys, and regardless of recent versus past reported exposures. And at least for HIV prevalence that's true in this recent versus past exposure.

Similarly, HIV prevalence in injection drug users remains high, although there is greater geographic variation. And in women exchanging sex

for money or drugs, they continue to have high prevalence of HIV, also across different venues and geography.

Thank you very much.

(Applause.)

DR. DAYTON: We'll move along to the next presentation now. Bernie Poiesz will give a talk on prevalence and incidence of HTLV in high-risk behavior groups.

DR. POIESZ: Thank you. Dr. Jaffe has already done a nice job in introducing the topic. I'm asked to concentrate on discussions about HTLV I and HTLV II, which, as you can see, are members of an oncogenic genus of retrovirus that also contains bovine leukemia virus.

We have developed a convention of referring to this group in its toto as the primate T-cell lymphoma leukemia viruses, because, as was mentioned, the genetic overlap between simian strains of this genus is quite frequent. And you really can't separate the strains by species; you have to separate them by geography and temporal dissemination from each other.

As was mentioned, HTLV I causes a variety of diseases, most notably adult T-cell lymphoma leukemia, but also myelopathy,

polymyositis, Sroegen's syndrome, and perhaps a variety of other autoimmune diseases. It can cause a low degree of immunodeficiency, and half the patients that present with HTLV present with opportunistic infections and quite often die from that, but certainly nowhere near its distant cousin, HIV.

HTLV II probably does cause some finite amount of disease in humans, but it has to be extremely rare. We've been involved now in working up in toto, in the entire history of our laboratory, eight cases of CDA positive T-cell lymphoma which we believe are caused by HTLV II, as opposed to thousands of cases of adult T-cell lymphoma leukemia.

We've also been involved with identifying approximately 20 patients who have a neurologic disorder that is quite similar to HTLV I, except that the area of greatest involvement in HTLV I seems to be the thoracic cord, whereas in HTLV II it seems to be the cerebellum and the cerebellar tracts, such that the patients present with a cerebellar ataxia.

We're involved in large studies in endemic groups in paleoAmerindians to try and really

identify the true incidence and prevalence of disease.

HTLV I causes disease in about four percent of infected people over their entire lifetime. However, if one is infected perinatally, the lifetime risk for developing adult T-cell leukemia goes up to about 10 percent; hence, one of the major pushes to stop perinatal transmission.

To my knowledge, no one has developed adult T-cell lymphoma leukemia from an HTLV I infection that occurred via blood transfusion, although certainly people have developed HTLV I associated myelopathy; and, in fact, have developed it in a very quick timeframe. The earliest that I know is three months post-transfusion. So that seems to be the major risk. But, of course, if you transmit it via transfusion, then the chance of transmitting it to other people and getting that perinatal infection goes up.

I want to talk a little bit about the biology of this genus of retroviruses because it is clearly different from HIV. It replicates very slowly. It's hard to transmit it, and its efficiency of transmission is about one one-thousandth, that of HIV. And it expresses its RNA and proteins to a very low degree.

As you'll see, the point I'll make is that if you want absolute sensitive detection of this group of viruses, serology assays probably won't do it because in some people there either are defective viruses or a very slow latent period in terms of expression such that seroconversion can take a long period of time.

This is another phylogram showing you the BLV genus group here, and the HTLV I or PTLV I group here. This is the human group of HTLV II. Mixed in here are several simian strains of STLV I's, and they just overlap. I'll show that a little clearer in another slide.

These are two new members of the genus that have been identified in the past couple of years. Primate T-cell lymphoma virus long has been found in Entrean baboons whose previous geographic range was southwest Asia and northeast Africa. This is STLV II, which is found in pygmy chimps in Africa.

All of the HTLV II's identified to date fall in a very close group, no matter what human, in what part of the world, even Central Africa; they seem very close to those strains found in paleoAmerindians. The HLTV I's and simian strains are divided into two groups: those in Africa and

those in Asia, Australia, and Melanesia. To date, no one has found a human counterpart to PTLV I or to STLV II, but I would submit that perhaps people haven't looked enough and they may exist.

Among the genus, divergence of one percent takes about 500 to 1,000 years of separation, so there is relative conservation making development of degenerate or generic assays somewhat easier than it is for HIV. There is very little evidence for recombination. Although I don't have time to show you, we now have evidence that modern BLV represents a recombination of something between STLV II and PTLV I, with an H and PLV.

It's important to note that because we now know that we have many intravenous drug abusers who are co-infected with both HTLV I and HTLV II, and, to my knowledge, no one has looked to see if recombination has occurred and what would be the biology of such a recombinant strain. We know that out in areas where there's different strains of HIV recombination occurs in about 10 percent of the isolates looked at.

Most of the serology strains used to look for antibodies to HTLV I or II are developed from a West African HTLV I isolate. Recently, people have developed recombinant peptides from the

West African strain to add to the assays or from an HTLV IIA strain. And very recently, Abbott Laboratories has used an HTLV II strain to add to the HTLV I antigen to broaden the mix.

But you can see that there is relative divergence among these, and absolute cross-reactivity might not occur. There is approximately 40 percent divergence between HTLV II and HTLV I, and about 60 percent to BLV.

Now, I want to talk about the biology of the virus and the differences between HTLV and HIV. Again, HTLV has gotten into humans, into primates, tens and tens of thousands of years ago. And over time, evolution has probably resulted in a more symbiotic relationship than we see with HIV 1.

One of the differences between HIV 1 and HTLV is the presence of complete retroviral DNA transcripts in the virus. We now know that HIV is capable of full reverse transcription in an extracellular mode, not to the degree of the hepatitis B virus -- remember, hepatitis B virus is a retrovirus in disguise.

It replicates to an RNA intermediate, but, intracellularly, almost completely replicates its DNA into a double-stranded DNA, finishes that extracellularly. That's, in part, why your

multiplicity of infection and your transmission rate for hepatitis B virus was higher than HIV. And HIV does this to some degree; HTLV does not do it well at all.

Proviral DNA may. You get one copy of DNA for every 10^3 copies of HIV RNA; whereas, for HTLV you get one copy of DNA for every 10^6 molecules of viral RNA. So there is roughly about a thousand-fold difference in transmission.

We now know in our laboratory we've at least studied this. This is the reverse transcription step, and it can kind of be broken up into three parts. Viral RNA starts as a single-stranded RNA, and there is a tRNA primer here that primes what's called strong stop DNA synthesis. That RNA then gets degraded by the viral RNA's H, and this strong stop DNA has to make a jump to this end of the viral RNA where its complimentary to the repeated sequences. And then first strand synthesis occurs, then there's more degradation, and eventually full length.

We can make primer pairs and do PCR to look for these various components. We now know that HTLV makes strong stop DNA about one-tenth the efficiency of HIV. It makes the first jump at about one one-hundredth the efficiency and full length at

about one one-thousandth. Somewhere in here is the major block in HTLV replication relative to HIV.

Obviously, therapeutically, if we could identify these molecular reasons, we might be able to design attack points to make HIV behave more like HTLV and slow down its transmission. But this, in part, explains why HTLV replicates so slowly.

After the viral DNA gets integrated, in HIV there is relatively rapid transcription of the RNA, and modulation of splicing patterns that is different than what we find in HTLV.

In all of the complex retroviruses, there is regulation of splicing. Initially, when a viral RNA transcript is made, the complete primary transcript is synthesized. In both HIV and in HTLV early infection, this RNA is quickly spliced down to multiply-spliced or singly-spliced molecules.

The multiply-spliced RNAs encode for these proteins. In HTLV I, it's TAX and REX, and a variety of others, the single splice for the envelope, and the primary transcript for the GAG/POL proteins. In your antibody tests, the major proteins are the GAG and the ENV proteins. In HIV, there is rapid progression from dominant multiply- and singly-spliced messages to making unspliced

message and making infectious virions and making all of the proteins.

In vivo, it has been noted that asymptomatic patients will tend to have these dominant species, and then as they go to symptomatic make more of the primary transcript.

In HTLV, the opposite is true. Both in vitro and in vivo, the dominant species, one hundred to a thousand-fold over the primary transcript are the singly- and multiply-spliced RNAs. HTLV-infected cells simply do not make a lot of retroviral virions, and they don't make a lot of GAG protein; hence, they don't stimulate antibody production to the major protein that we have in the assay.

When you use the purified virions to make an antigen prep for the serology assay, there is also a great difference because of these problems in replication, or differences in replication, between HTLV and HIV. The antigen preps are made by purifying virions from cell culture condition media. Again, in that media, there is roughly about one one-thousandth the content of HTLV virions per cellular debris than there is for HIV. So the viral protein to cellular debris ratio is off quite a bit, and your preparation is not as pure.

The other thing is that in HTLV purified virions, the envelope proteins gp46 and gp21E are deficient. Now, we know that the cells make them to a varying degree, because if we do RIPAs we see them there. But somehow they don't get incorporated into the virion to the same degree that HIV does.

One of the reasons is that HIV has a regulatory gene called VPU. VPU's function in the golgi apparatus is to degrade the cd4 protein and message such that receptor for HIV glycoprotein is not present, allowing the envelope protein to make it to the surface. HTLV has no such gene, and it doesn't down regulate its receptor like HIV does.

So when you make an HTLV virion, it is relatively deficient to its GAG proteins in this envelope protein. And if you look at a Western Blot on some of the classical assays that are FDA approved, unless you put a recombinant envelope protein in there, you won't see any reactivity to an envelope. So it's a major difference.

In HTLV I, some of the non-specific reactivity in normals is against the p19 and the p21. We now have data that part of the reason for this is we all contain endogenous retroviral sequences in varying amounts and in varying different sequences and varying degrees of

expression during our lifetime that have homology to these two proteins.

The epitopes have been identified in p19, and the epitopes for cross-reactivity have been identified in p21E. And if you make peptides that do not encompass those overlapping epitopes, you get a much better preparation.

Gene Labs made a Western Blot with an epitope called GD 21, and that's actually a very good, very specific epitope. They have another one called BA 21 that cross-reacts in about seven percent of normal humans and higher in certain diseases. But probably to make a better HTLV I antigen relative to HIV, you probably are going to have to depend more upon recombinant proteins and peptides to fill in these gaps of deficient proteins and to try to avoid some of the overlapping sequences that may be expressed by endogenous sequences.

To look for HTLV I in a sensitive manner, in my opinion, you have to do PCR for DNA. It doesn't help to do PCR for RNA, because HTLV I, HTLV II, BLV-infected animals do not express a lot of RNA. Our range of detection for RNA is such that only about 60 percent of infected individuals have detectable RNA in their plasma, and the copy numbers

range from anywhere from 10 to 1,000 per ml, where the copy numbers for HIV will be in the hundreds up to ten million. So it's very rare to find high copy number viral RNA expression.

We've done -- one of the problems with PCR is making it sensitive, making it multiplex so that you can look for variety assays, and making it specific. In terms of sensitivity, we have collaborated with the folks at Johnson & Johnson, and they have developed two monoclonal antibodies against the DNA polymerase, Taq polymerase. And when the antibody is added it activates the Taq polymerase.

This prevents false primer extension should your viral primers anneal to something in the human genome that has some homology, all right, and dampen your productivity. If we add these antibodies, we get approximately a thousand-fold greater yield in our PCR product after about 40 cycles.

So it enables us to do sequencing a lot easier, but it has made all of the assays robust, such that we can usually develop a PCR assay for a known human retrovirus that is sensitive down to one copy per aliquot in a Poisson distribution, i.e. 60

percent of the samples at that concentration will be positive, the maximum sensitivity.

Another problem is carryover. If you amplify the DNA in an open lab, open everything up and then try to go detect it again in another person, you'll start getting false positives from the synthetic DNA that you've made and aerosolized in your own laboratory.

In our laboratory, and with the data I'm about to show you, we have physically separated the pre- and post-PCR people, equipment, personnel. They're actually in a separate building. That helps. We also use uracil N glycosylase. We incorporate DUNP into the synthetic DNA and can presterilize that DNA by treating it with uracil N glycosylase, which hydrolyzes the synthetic DNA.

The other thing we do in our primers -- we add linker sequences on their 5 prime end, such that all of the synthetic amplicons have this non-human/non-viral DNA at their tail. And we go back and make primers just to the yellow portion, the non-viral portion, and scan our samples to see if we have any false positive. A negative result would suggest that our positive result before on the human sample with the viral-containing primers is a true positive.

We have recently collaborated with Fred Kramer at the Rockefeller Center to develop a system and test it in human retroviruses. I think it solves a lot of these problems. They have worked with beacon probes. They can do PCR now in a single tube that doesn't have to be opened from start to finish. You can throw it away at the end and can multiplex several different assays, both for sensitivity detection and for quantification over several cycles. The capacity at the moment is up to 28 simultaneous targets, either 28 different strains of HIV, 28 different resistance molecules, or 28 different life forms at any one time.

The beauty of this is that their probe can be silenced completely. The business end of their detector sequence is shown here in the circle, and it has a tail on either end. The open circle is a fore, and the dark circle is a quench. When it doesn't see its target, kinetics are such that it wants to stay in this stem loop structure, and that brings the quencher close to the fore and completely inactivates it.

When it sees its target and hybridizes, however, the fore is now removed from the quench, and you have light. You go from dark to light. And the background noise is extraordinarily low, such

that you can add all of this in the beginning and it starts to hybridize as you do each PCR cycle.

This just shows you results with HIV 1, HIV 2, HTLV I, and HTLV II. We have very sensitive detection of these. We can mix and match them. We could look for different strains and get very robust amplification. We made primer pairs to all of the known strains of HIV and all of the known strains of HTLV. And at least what was in the literature we could find all of the known variance that exists in the world, to our knowledge.

We're actually in a position now of making mutations. We're making random mutations and selecting out viable mutants to try and see if there is anything that can escape our primer pair system now. We're going to make them, rather than go out into Africa and find every strain. We're going to make them in the lab, and we've proven you can do that.

It's also linear and quantitative over a very long range. It's hard for you to see, but this is the multi log of linear range because of where you're starting at. So quantification occurs -- the cycle that the background -- the signal comes off the background noise determines the copy number, and

the range is almost over a million-fold. So it makes it very suitable for quantification.

As for some actual results -- again, I'm not an epidemiologist, so I have some prevalence slides. I'll talk about some incidents as I know them, and I'm probably not as sophisticated as some of the other speakers.

HTLV II is endemic in paleoAmerindians. We have been collaborating with Dr. George Ferrer and Eduardo Esteban, studying the Indians of the Gran Chaco plateau in South America. This is the plateau that skirts northern Argentina, Paraguay, and Bolivia, and it is made up of two major linguistic and genetic groups of Indians. They have a very high incidence of HTLV II and prevalence of it.

Now, as I show you this data, this is not the entire tribe, and it's fair to point out that this is us going and looking at family members and sex partners and children of some of the initial infected people. So the prevalence rates will be quite high.

We used a variety of screening ELISAs; again, made primarily with an HTLV I Western Africa antigen prep that we used to select ELISA which can discriminate between HTLV I and II. And at this

point in time, we used the Gene Labs' 2.3 Western Blot that does not contain that GD 21. And we did PCR from a primer pair that's conserved in HTLV I and II POL gene.

This is the sensitivity and specificity on Indians that we found. You can see that the screening ELISAs, etcetera, have a relatively low sensitivity relative to PCR, but that PCR was not a hundred percent. The specificity of the screening ELISAs vary. Actually, the lowest one was removed from the market, in part because of that. The select ELISA -- and the Western Blot is how we interpreted reactivity to p24 and gp46 being a positive -- was quite specific and the PCR was quite specific.

Now I'll show you similar sensitivity results, if you can see them, in a variety of groups at risk for HTLV I or HTLV II. These are American IV drug users, irregardless of race, and they had a 14 percent positive rate. And the serology assay was about 89 percent, and the PCR was 98.6 percent. The people who were seronegative tended to be those who have picked up their IV drug abuse relatively recently. And when we came back to them and followed them two years later, about 10 percent of the seronegatives had seroconverted.

In sub-Saharan Africa, the prevalence rate was 11 percent. Again, the serology is 93.8 percent, and the PCR was 100 percent. In paleoAmerindians, we've studied three major groups -- the seminole, the Yaruro Quahibo in Venezuela, and the Toba and Matako Mataquaqan in the Gran Chaco. And again, you can see the serology results go anywhere from 71 percent to 83 percent sensitivity, and the PCR is 97 percent to 100 percent.

The point being, that if you really want to find all people infected with HTLV II, or all people infected with HTLV I, you pretty much have to do both assays in order to pick them all up. A number of labs have done this now, and I think it's a believed truth.

We have also done this in animal models. Part of the variation -- we find that we now know the receptors for HTLV I. We have identified that humans and animals have different alleles for this receptor. And what we don't know is whether those alleles correlate for different rates of infection, etcetera.

This is the prevalence rate in various groups that we've tested for HTLV I or II. This was done approximately about five years ago, so it

doesn't reflect recent data. And here we're calling them positive if they are seropositive and PCR positive. Remember, if we probably had done PCR in all of these people, the prevalence rate would be slightly higher.

This is a volunteer blood donor group. It's predominantly blood donors in the northeast, and the prevalence rate was about .02 percent. One person was HTLV I; the other person was HTLV II. You can see in paid blood donors that the prevalence rate goes up higher and it's statistically different.

We studied caucasian IV drug abusers to eliminate the background noise of HTLV I being endemic in black people. And this is predominantly IV drug abusers in the Syracuse and New York City area. And you can see the prevalence rate there was about four and a half percent.

In studying caucasian prostitutes in New York City and Syracuse, we didn't find any of them infected.

This is -- we've got homosexuals, hemophiliacs. Again, this is predominantly caucasian homosexuals and hemophiliacs in the central New York and New York metropolitan area. And only one person was positive -- a homosexual.

The hemophiliac data points out what Dr. Jaffe alluded to. With Alan Williams, we have done studies in the past and looked at people who have gotten seroproducts, either Factor VIII, that were hemophiliacs, or immunoglobulin preps. We find no evidence of plasma products ever passing HTLV I or II. The transmission rate of HTLV I or II via cellular products occurs, and it depends upon the amount of blood that a person received and the timing of the blood. Those blood products that were stored for more than five days tended to have less of a transmission rate.

In family members and sex partners of HTLV positive, you can see the rate was about 13.6. The data, if you follow these people, are that in babies born to mothers who breast-feed for at least two years, the transmission rate is about 30 percent. If you cut off breast-feeding at about six months, the transmission rate drops considerably. And, in part, this has been suggested to be due to a decrease in neutralizing antibodies in the breast milk to the virus.

In Japan, where they have identified -- in southern Japan, where they have identified most pregnant women as being HTLV I positive or negative, and mandated that those women not breast-feed, the

maternal transmission rate has dropped down to less than one percent. So that seems to be a significant thing in another part of the world where you can affect the use of breast-feeding in positive women.

In sex partners, the transmission rate male to female is greater than female to male. And in life partners over their time, from someone who we believe was infected perinatally, the transmission rate is about 30 percent to their sex partner, if it's male to female, and about 10 percent if it's female to male. But per year, the transmission rate is very low.

Needle stick victims -- we had a contract with the NIH and a variety of other groups to look at all of their HTLV-related accidents, where people had jammed themselves with a needle or pricked themselves, etcetera. These are the first thousand people. We have not found anyone that has been infected via that route, so it must be relatively rare, if it occurs at all.

These are black people coming to medical clinics in Brooklyn. It doesn't necessarily reflect the general black population of Brooklyn, but people coming to a medical clinic, and the prevalence rate there was around four percent. When we looked at the same type of group in central New York, the

prevalence rate dropped to 1.2. And if we looked at caucasians, the rate was much lower.

And then this just represents the study within the cancer acute leukemia group B, to look and see how many HTLV I related lymphomas or leukemias are occurring per unit of time. So over a six-month period, we collected a variety of patients with either CML or AML, ALL, CLL, and found none of them to be infected, even though they had gotten blood transfusions both in central New York and mostly metropolitan New York City.

Others have probably looked at an earlier population where screening for blood may not have been drawn on, and in that population that had received a lot of blood transfusions have identified infected people. This occurred after we had testing for HTLV I, and that seemed to have solved that problem.

In our lymphoma group, we found eight positive people, and they were all in the other than low-grade, non-Hodgkins lymphoma for a prevalence rate of four percent in that group, which we would suggest is probably the prevalence rate of that disease in other than low-grade lymphomas in the United States.

So I'll stop there. It's clear that there are risk groups for HTLV I. If you want to monitor them, serology and PCR seem to be required.

Thank you.

(Applause.)

DR. DAYTON: Thank you very much, Dr. Poiesz.

We're going to take about a 10-minute break now, and then we'll try to fit in a panel discussion afterwards, if all of the speakers who spoke this morning could join us up at the front table here.

(Whereupon, the proceedings in the foregoing matter went off the record at 10:39 a.m. and went back on the record at 10:52 a.m.)

DR. DAYTON: If we could begin to get organized, settled, we'd like to begin the panel discussion. And I'd like to invite all of the previous speakers to take a seat at the table.

We thought we'd get things started with the panel discussion by just reviewing some of the general questions that we have, basically general questions which are the theme of this workshop. And I can read them, if -- and I'll just read them fairly quickly.

In the face of sensitive tests for HIV, HBV, HCV, and HTLV, should men who have had sex with another man even one time since 1977 -- that's A, or B, people who have had sex for money or drugs since 1977 -- you can see that the language of this largely comes from the HIV epidemic -- C, people who have ever abused intravenous drugs, and, D, sexual partners of the above, should these groups be deferred for life?

Another general question is: what lessons have we learned from prevalence and incidence of the diseases we have discussed today in individuals who engage in these activities with respect to blood safety. Obviously, this is very closely related to the question we just went through.

What lessons have we learned from emerging infectious diseases in individuals who engage in these activities, with regard to blood safety?

So if I can encourage any of the speakers to either volunteer to get things started, or perhaps we could start with a general discussion. As I was discussing with Harold Jaffe during the break, what do we do with unknown diseases? And, of course, that's an almost unanswerable question, but

it -- on the one hand, we -- as Dr. Jaffe pointed out, each new pathogen or each pathogen can behave very differently in its rate of transmission through various modes, even if it share modes of transmissions with other pathogens.

And how do we handle this in terms of, do we consider certain high-risk behaviors that are high-risk behaviors for several pathogens? Do we justifiably consider them as high risk for unknown pathogens? Is there anybody who -- Dr. Jaffe, would you care to comment on that? I'll put you in the hot seat.

DR. JAFFE: I think I've been set up.

DR. DAYTON: Absolutely.

DR. JAFFE: I don't know the answer. It seems to me, you know, reasonable to think, though, that injecting drug users would be at risk for any blood-borne pathogen, almost by definition, if you're injecting a contaminated syringe into your own body that you would be exposed.

So I think that's probably a safer assumption than to say that any agent which has been shown to be -- or any member of a group of agents which has been shown to be sexually transmitted, that other members would be sexually transmitted as well. So I think it's a safer bet to think that

injection drug users probably are going to be at risk for future emerging blood-borne infections, and that it would be harder to generalize about sexually-transmitted infections.

DR. POIESZ: I would say, number one, it's pretty evident that we keep getting pathogens introduced from some other source, other than humans, episodically over our lifetime as a species.

The other thing is that all of these phylograms that we're putting up there, the one thing we didn't have time to get into, if you actually work out the mathematics and the degree of divergence, the degree of mutation that they have per unit of time, there is things that are missing on those phylograms.

You saw my thing with the BLV. We looked at cattle across the world, dairy and beef cattle, and the total divergence is only six to eight percent. But the other side of the node, we have HTLV I and HTLV II that are 40 percent divergent. And yet every mathematical calculation we make says that the BLV side should have mutated to the same degree as the PTLV side, and yet we don't find it.

Now, nobody has gone to yaks, water buffalo, etcetera, and looked for these other

strains or looked at other primates for them. But there have to be either extinct strains on that side of the phylogram or they're still out there. And what they would do to man we don't know, but there have to be a lot of other strains that can fit on those phylograms.

The same for HIV. And if you do it for hepatitis B, hepatitis C, you come to the same mathematical conclusion. So I'd say that one thing you could predict is there are other variants out there of these known groups.

DR. IAN WILLIAMS: One sort of caveat I guess I'd add from the hepatitis B and C perspective is is the hepatitis B and C have been around probably for long periods of time. Hepatitis B has probably been around -- is a relatively ancient disease. And the data on hepatitis C is a little less sure, but there has been at least one study that found hepatitis C in a group of Air Force recruits as early as the late 1940s.

So when you think about putting date limits on questions, you have to consider that some of these diseases have been around much earlier than HIV. So it's somewhat artificial or something to at least consider when you think about hepatitis B and C.

DR. DAYTON: We had some questions from the floor, I think. Did you --

DR. IAN WILLIAMS: We have at least one question, and the question is: can HCV be transmitted through close contact within households? The answer is yes, probably, but it occurs very, very rarely. Basically, our current recommendations say that household members shouldn't share anything that could potentially become blood contaminated, such as toothbrushes and razors or anything that could become blood contaminated. And if you have open cuts and sores, you should keep them loosely covered.

This is more of a response to the fact that -- a theoretical risk rather than we actually see transmission occurring by these means. And the bottom line really is is that yeah, transmission could occur, but we really don't see it. So, you know, hugging, sneezing, kissing, all those sort of things that cause general public concern do not transmit HCV. And probably a little common sense about exposure to blood is warranted in the household setting.

DR. DAYTON: Thank you.

I'd be very willing to open this up to questions from the floor. If anybody has any questions, just go to the microphone.

Jay?

DR. EPSTEIN: I believe it was Dr. Steketee who showed us a graph of prevalence of various markers split out by whether there was history in the last year, or I guess it was lifetime history. And although the slide went by quickly, it looked as if there were no significant differences. And I wonder whether that observation has any implication in your own mind about the question of lifetime versus temporary deferrals.

DR. STEKETEE: Yeah. I think basically the answer is that picking a specific year for when risk began was used for HIV largely because we had a time when we thought HIV was introduced in the population. And as you just pointed out, HCV and HBV have been around for a lot longer than that.

So our data right now suggest that there is no clear year to pick when somebody had recent behavior versus long-since-past behavior that would help us.

And let me -- I'll make an additional comment. Going back to Andy's -- one of his opening slides about using tests to intervene between the

selected blood donors and eliminating any possible infections in that pool, and then using questionnaires to get us a suitable donor population. And what I would suggest is that given the prevalence of HIV and incidence of HIV are high, what we have done in the past is that we initially set out donor suitability criteria as the first gate, and then used tests and have spent an enormous amount of time trying to use tests to get -- to find those incident infections because we had a fairly good test and we have used donor suitability criteria in order to reduce the prevalence in the population of acceptable donors to such a level that we could account for all of the prevalent cases with our test and then spent a lot of time on the incident cases.

If we change the prevalence in the population by relaxing criteria and hoping for the test to pick up all of the prevalent cases, then we double the indemnity on the test. And just -- I think that's what our data would suggest. There's not a year to go back to, and the prevalence is still high in those traditional risk groups that we've accepted and have requested that they self-identify and self-select out of the donor pool.

DR. DAYTON: It's interesting that you mention that you would double the indemnity, because when we did the MSM calculations about a year ago for BPAC, and actually assembled a group that did a great job putting together the numbers, that's about what we came up with is that you essentially double the indemnity, even though you don't know what it is.

DR. BIANCO: I would like to hear ideas from the panel. I'm not sure that I agree entirely with those calculations because they make the assumption that at these points people would tend -- that people that have this continuous type of behavior, that have chosen this is a lifestyle, would have ceased performing during the last year. So I think that we will have to introduce that.

But the question, actually, that I wanted to ask is: I know that we are going to hear, particularly from Dr. Williams, questions -- issues about sensitivity and specificity of medical history. But in all of the experience that you have in surveys, in epidemiological surveys, and all of that, could you give us an estimate of what is the sensitivity and the specificity of medical history?

Because we are basing all of those things and all of these theoretical deferrals for

preventing an emerging infection, and all of that, on asking a question of a donor. And I'd like to see if we know more about it.

DR. DAYTON: You're asking how effective are the questionnaires, basically. And actually, we're going to get into discussing that later in the day. This is an absolutely relevant question.

DR. STEKETEE: I'll make a comment, though. I mean, there are several layers of this. One is that we have asked -- in public education, we've asked a large number of people to self-identify and never even come to the table to be asked the questionnaire.

And so by definition, you know, for example, if you say that we've asked men who have sex with men since 1977 to self-identify and never come to, you know, the donor setting, then those people who do come, you have a certain level of sensitivity and specificity of that questionnaire. But it's not the same as if you just ask all of the population, not having asked them to self-identify and self-select to begin with. So while it's a relevant question, it changes if you relax the criteria for everybody donating.

DR. IAN WILLIAMS: I can add maybe a little bit of data that's sort of a different

setting. We look at people that are acutely ill with viral hepatitis and interview them. We think that on the ballpark of roughly 30 percent of people basically are not being truthful for us when they interview. However, they admit to a whole broad range of risk factors, just not sort of bad risk factors. I'm not a current injector, but I used to. That's not a problem.

And we hear anecdotal stories over and over again about a patient will have track marks on their arm and totally deny admitting injection drug use. It may be different in a donor setting, but we think that in the ballpark of about 30 percent of people.

However, we hear in other settings the more you interview people, the more the truth comes out. This is especially true with hepatitis C in a prevalence setting where you have someone who totally denies injection drug use until they develop a relationship with their provider. And then, six months later, they come out and say, "Well, yeah, I used to inject, but don't ever tell anybody because I'll lose my job" sort of thing.

So it's a sensitive subject, and I don't know if there's an answer. It depends on the

setting, how you ask the questions, how the interviews are done.

AUDIENCE PARTICIPANT: With respect to emerging pathogens, do you think that we should consider animal handlers or handlers who are exposed to animal bites or scratches as at high risk for blood donation?

DR. JAFFE: You know, I actually think that's a very interesting question. In the article that was published on the foamy virus infection, the point was made that about two percent of -- it's a relatively small sample, but about two percent of people who professionally worked with these non-human primates were actually infected with these foamy viruses. So, I mean, that's really quite substantial compared to a lot of other groups that we think are at increased risk for this or that.

So in terms of being at risk for those viruses that are endemic in non-human primates, such workers probably should be considered at increased risk.

DR. ALAN WILLIAMS: One comment, just getting back --

DR. DAYTON: Actually, I've had a request for everybody to identify themselves when they speak, Alan.

DR. ALAN WILLIAMS: Sure. Alan Williams, Red Cross Holland Labs. Just to get back to the questionnaire screening again for a moment, in the interviews done with donors found to be positive for infectious disease markers, typically risk factors are found and they're related to denial of the risk factors at the time of the screening, rather than inadequacy of the screening criteria. So I think that basically becomes the crux of the issue.

And a comment I want to make, which I was going to save for this afternoon but I'll go ahead and make it now, and that is if the screening criteria are changed, one can't necessarily assume that the failure to defer is going to be a constant on either side of that change, because there are other factors at play. And I can see inherently this going one way or the other.

For instance, if the subpopulation under consideration feels that a certain criteria is not scientifically justified and may, in their view, be discriminatory, then it might have a reaction in one direction. On the other hand, if screening criteria are relaxed and the less savvy donor views this as being more and more reliance on the highly sophisticated screening test, there might be a push

in the other direction such that, you know, inaccuracies could occur as well.

There are very few data to address, you know, the potential dynamics of this. But I wouldn't necessarily assume that the failure rates are going to be both -- going to be the same on both sides of the equation.

DR. DAYTON: Thank you.

MR. DODD: Roger Dodd, American Red Cross. I'd like to pick up and go back a little bit to something that was inherent in the questions that you showed, Dr. Dayton, and that was the issue of since 1977. The panels discussed that there really should be no starting date, and part of the issue, I believe, the last time this came up at the Blood Products Advisory Committee was, is since 1977 an appropriate category of questions to ask. Should it, in fact, be in the last year or ever, since there seems to be little continuing rationale for the use of 1977? And I wonder if that is actually discussable.

DR. DAYTON: Well, that's discussable. I'm not sure I have an answer. I certainly think 1977 makes sense with respect to the AIDS epidemic. Whether you want to get worried about other pathogens is an entirely different story. And,

really, the answer to that is going to come from the data that's presented here, at least as close as we'll get to the answer.

Mike?

DR. BUSCH: Yeah, Mike Busch. A couple of comments. I think in terms of the timing issue, I agree with the comment about, you know, if we relax criteria the prevalence will go up. We'll basically allow people to come in in whom remote risk would have allowed infection to have occurred long ago, and, therefore, they would be prevalent infections.

And I think the options to get around that, such as persons who have remote risk, perhaps putting them through the screening system first independent of donation -- I mean, the only indemnity, believing all of our data which supports that the tests are actually very accurate at picking up prevalent infections, which I think they are, the only compromise there is the potential of a test error occurring. And if you put people through the system twice, for example, you could test them in to becoming eligible as a donor.

So, to me, the big concern is the emerging agent, your new HIV epidemic. And I think what Harold showed -- you know, we didn't know AIDS

existed for over five years from the point where it was beginning to explode in the population is kind of the fear that we all are struggling against.

On the other hand, FDA is overreacting to every rare variant and making us fix tests for rare variants that, as Harold showed, probably aren't spreading at any significant rate, clearly aren't prevalent here. So it's a dilemma, and to throw the dilemma even further open, I mean, we now have two recent emerging agents or newly-described agents -- HGV and TTV -- that we know are prevalent viremic in our donor base, and that two to five percent of all current donors are viremic for these infections.

We're now just sorting out that they don't seem to cause disease, and they don't have -- clearly, these are prevalent in our donors. I don't know of any risk factor data, but they're prevalent at these extraordinary rates, despite all of these screening efforts.

So, you know, the concept that these old questions have excluded potential new and emerging agents effectively, I think, you know, that kind of data shows that that's just -- they're not working at excluding agents, and any of these could have been, you know, significant pathogens.

So I don't have any specific questions, but just the dilemma is really I think the emerging agents is where the problem lies. And I just don't think we have any handle that any of these risk behaviors that we're doing now are really going to effectively deal with what might be the next significant emerging pathogen.

MR. HOLMBERG: I'll try one more time. Jerry Holmberg, Navy Blood Program. I'll talk about remote risk and the emerging pathogen. What's the panel's opinion on a potential donor that presents that is a heterosexual in a monogamous relationship that has had -- their partner has used IV drugs maybe 10, 15 years ago?

DR. STEKETEE: You know, for HIV, I'll go back to Mike Busch's comment. You know, if people get tested separate from the blood donation system to determine whether or not they -- you know, so that you've got several screening levels, that's a group that might benefit from that because the prevalence of HIV in somebody who injected drugs 15 years ago is, you know, still not insubstantial.

And the likelihood of exposure of the monogamous sex partner to that infection, if it were HIV, is, over those 15 years, not inconsequential either. But you would want that -- you would

probably want that person screened outside of the blood supply so that an error isn't what is allowing them to get in on a single screening test. Hepatitis may be a different story.

DR. IAN WILLIAMS: Yeah. Hepatitis C is a little more vexing issue, because the role of sexual transmission is a little unclear. Again, the rate of transmission seems to be relatively low among long-term monogamous partners, and even so low that we don't recommend that barrier contraception be used routinely. It's a decision they have to make with their partners, so I think that shows our sort of level of uncertainty, but we think it is fairly low.

Again, it comes down to an issue of window period versus prevalent infections. And if the rate of transmission is fairly low, you're talking about relatively small probabilities. And I can't give you the answer to that; just to tell you that the rate of transmission is low and it makes it a very difficult thing to come up with an exact number to put probabilities on to make a decision.

DR. DAYTON: Jay?

DR. EPSTEIN: I just wanted to make a comment that as I listened to the first set of presentations, we tended to hear a lot more data on

prevalence than on incidence. That's for obvious reasons when you consider the methodological difficulties. But on the other hand, a major concern with depending on donor exclusionary criteria is that they are our most effective way to adjust the incident infection, putting aside for the moment the relative contribution to blood risk.

And I would just encourage the investigators to do what they can to focus on helping us with incidence estimates. For example, we did not hear an incidence estimate for hepatitis C in a sex worker, and yet that might be important to know.

So I think, Andy, you very well laid out for us the double challenge that we face in dealing with prevalent and incident infections, and I just have the reaction that we don't quite know enough about incidence compared to what we would like today.

DR. DAYTON: Does anybody want to respond to that before we --

ALL: We agree.

DR. DAYTON: I think, yeah, we all agree. Martin? Let's have one more question from Martin.

DR. RUTA: I was wondering if CDC -- actually, I had two questions. But, one, I wonder if CDC had comments about retaining the 1977 date for --

DR. JAFFE: Well, I mean, that clearly came from HIV 1, and it probably makes sense for HIV 1. But I think as all of the other panelists indicated, it doesn't make any sense for any of the other things we're worried about.

DR. RUTA: And a second question, which I think was partially answered. But, you know, we have different deferral periods. Some are lifetime; some are one year. Is it rational to base the deferral period on the relative risk from the type of exposure? Would you have any comments about partners of the activities that we talked about today, whether you have any thoughts on whether that should -- you know, it makes sense to have a one-year deferral period for partners of IV drug users, etcetera?

DR. STEKETEE: You know, with the one-year deferral period, I'll go back to Jay's comment. You're asking the question of prevalence in that situation versus incidence, because the assumption is that you may have a prevalent infection because they had past exposure. But because of the one-year

deferral period, you've tried to eliminate their recent infection, and, therefore, incidence and miss the incident infection.

I think while you want to eliminate, as much as possible, those incident infections, you have to look at the test capability -- we'll hear about that later as well -- but in terms of identifying prevalent infection and making sure. Because if you set the gate at just eliminating incident infection, you've got to have the test be very, very good, making sure you have no prevalent infections.

MR. HOLNESS: Les Holness, FDA. I just wonder if CDC has any data on individuals who have had sex change operations.

DR. STEKETEE: The number of people who have had sex change operations in this country is still relatively small compared to the population, and we have not historically asked that question in various surveys. And to my knowledge, that has not been done either at local levels or with CDC-sponsored surveys.

DR. DAYTON: Okay. Well, I'd like to thank the panel members for their time and their expertise. We're running a little bit late, so we'd like to move right along to the next speaker, who is

going to be Mike Busch, talking on prevalence and incidence in blood donors.

DR. BUSCH: Thank you. I'm going to be presenting sort of three separate sort of talks. And I'll just point out at the beginning that all of the numbers we're looking at here, you may get used to looking at them and thinking, you know, they are moderately high. You must recognize that they are one percent to one one-thousandth of the rates we were just talking about in the context of the CDC data.

The first analysis is an analysis from the REDS study group, and I want to acknowledge Simone Glynn and George Schreiber who are here, and Steve Kleiman, who have done a lot of work on this. And this is looking at overtime analysis of both prevalence and incidence in five U.S. donors.

We know that monitoring incidence and prevalence in the donor setting is important for the reasons we've talked about, particularly with respect to incidence in the window period, a little bit with respect to prevalence in test error.

And as we look at these changes in rates, we need to understand whether they are probably reflective of changing background epidemiology of the infection within the population,

changes in the criteria of selecting eligibility of the donors, and then we'll see also some examples where changes in the tests, either the screening or the confirmatory test, can actually fool one into thinking you have a change, for example, in incidence, but actually it's an artifact of shifting test methodologies.

This analysis is based on the five U.S. REDS centers, which are located in the Detroit, L.A., and Chesapeake, D.C., region of the Red Cross, and then in San Francisco and Oklahoma City, collecting about a million donations per year. And the markers that were focused on are the four major markers -- HIV, HTLV, HCV, HBV. We do, for both HIV and HTLV, review all of the data and exclude false positive results based on RNA tests, etcetera. Also, for surface antigen, we exclude false positive surface antigen results.

We're looking at incidence by looking at two-year incidence intervals. So especially when we try to break the overall period into subperiods to begin to look at incidence trends over time, the approach that the WESTAT group took was to actually combine two-year intervals and look over time at overlapping two-year intervals. This will become evident once you see the data.

Whereas, for prevalence, the numbers are large enough on an annual basis, enough where we don't have to accrue time in order to look at incidence, that we're looking at prevalence annually. So incidence is expressed formally as number of seroconverters per hundred thousand donor person years of followup, whereas prevalence is expressed as number of positives per hundred thousand first-time donations.

So in our analysis, we tend to always look at incidence in our repeat donor population and prevalence in the first-time donor population.

For HIV, just a little bit about the tests. We do include a period early on in '91 through early '92 when the screening test was the HIV 1 assay, and then we switched over to the HIV 1/2 Combi test, which is still the current assay. The data will actually continue through '96.

Now, this had no affect on detection because we -- I think in the whole country we've only picked up two HIV 2 infections after shifting to Combi. There was a slight window period reduction, but we looked at this data without sort of truncating the period, crossing the different tests.

Throughout this period, the primary confirmatory assay was the HIV 1 Western Blot from Cambridge Biotech supplemented by HIV 2 work. And the one twist here is that criteria did change early on. The criteria were actually more stringent, requiring three bands.

In February of '93, the criteria for interpreting the Western Blot shifted to allow a p31 band to not be required. This had two effects. One is it actually allowed detection of infection about a month earlier because the p31 band takes about a month to mature after the person is detected by the screen and has two bands in the Western Blot, and then the previously required p31 band takes another month.

So it theoretically could have increased prevalence or incidence due to the increased sensitivity of the confirmatory test. The other problem is it introduced a problem with false positive Western Blots, but in these analyses those have been excluded.

Okay. I'm going to show slides that are kind of like this -- tabular formats -- but then I'll also show the graphs to give you a better sense of over time trends. So what this shows is both the incidence, again, in these two-year overlapping

intervals, so '91 to '92, and '92 to '93, and then the prevalence per year.

So, for example, to just be a little bit straight, we'll just start with prevalence for HIV started at about 30 per 100,000, and it actually has declined to about 18 per 100,000 in '93/'94, and then has dropped actually to 15 per 100,000 in '96. So we've seen a highly significant decline in the prevalence of HIV in our first-time donors.

The incidence has dropped slightly from 2.6 per 100,000 person years down to around 1 to 1.5 per 100,000 person years, but that's not significant. So here you can see this decline in prevalence, which is highly significant among our first-time donors, and then a slight decline in incidence but it is not significant. So incidence, really, for HIV has remained relatively stable. But again, to emphasize, these are rates that are, you know, two to three orders of magnitude lower than background prevalence and incidence in the population.

With HCV, we started out data set for analysis with the introduction of second generation HCV antibody assay, and this is because the first generation test was missing around 20 to 30 percent of the persons who were actually chronically

infected with HCV. So when we shifted from the first to the second generation assays, there was a dramatic increased detection rate, which in a simple analysis would have implied a dramatic increase in incidence, because a lot of repeat donors who were negative were now detected as positive.

And to avoid that sort of misinterpretation, we only begin our analyses for this purpose with the second generation assay. And, in fact, with the third generation assay being introduced, there was a similar increased detection rate, although virtually all of the increased detection by the third generation tests were actually remote cleared infections.

But, again, there is some debate going on in the discussion section today that that actually did, in a similar way, artifactually drive up the apparent incidence, because donors who were actually remote infections began to be detected as apparent seroconverters on the third generation assay.

So for HCV, therefore, again, we've truncated the analysis to just look at the period after second generation screening began and before the third generation test began.

What we see here is prevalence running substantially higher than HIV. This is 600 per 100,000, so about six per thousand first-time blood donors positive. And this has dropped to about four per thousand now blood donors, first-time blood donors testing positive. So a highly significant decline.

Incidence has run around five per 100,000, and it has kind of bounced around. But it has really remained relatively stable.

So here you can see the significant drop in prevalence of HCV among first-time blood donors. Really not clear. The questions haven't changed that dramatically. Perhaps a focus of discussion: why have we accomplished this? Perhaps it mirrors what we saw from CDC -- the underlying drop of infection in the general population.

And then incidence, again, just kind of stable, again, at around three to four per 100,000 person years.

For HBV, we've pretty much been stable with a constant screening and confirmatory test during the period of this analysis through '96. And on our first-time donors, we're running in the range of 200 per 100,000, or two per thousand first-time donors are confirmed surface antigen positive. And

this has really remained fairly stable over the period of time.

Incidence for HBV has declined slightly but not significantly from around 7.5 per 100,000 years to around five per 100,000 person years. And graphically, again, the very stable prevalence among the first-time donor population, and a slight downward trend, but not significant, among the repeat donors.

HTLV -- during this period of time, the screening test did shift. Actually, during this period, the screening didn't. We were going from a -- well, there was a first-generation Abbott EIA, HTLV I based, and this was slightly enhanced in a second generation version of the HTLV I assay. It was not a shift to the HTLV I/II, which occurred more recently and is not part of this analysis. This test did have slightly improved detection based on the data submitted to FDA for HTLV II, but it is not a bona fide HTLV II test.

The problem with HTLV II that we faced is the confirmatory testing has shifted, and, fortunately, in a backwards direction. We used to be able to detect infected donors with a combination of Western Blots, and generally people were using recombinant antigen spiked Western Blots,

supplemented in people who were not positive with these -- for envelope in the Western Blots by doing radio immuno precipitation assays, or additional envelope typing assays. And these were the basis for the data in the first three years or so of the analysis I'll show.

And then a couple of things happened. The Red Cross confirmatory test laboratory began to be scrutinized by FDA, and actually backed away from using some of the less established assays, such as RIPA or peptide EIAs, and went to a single assay, the p21E spiked Western Blot, which was under IND. We still don't have a confirmed assay, confirmatory licensed assay for HTLV.

And the problem here is this test we know has the problem with false positivity that Bernie talked about. This envelope antigen in here is not specific, and we know that some small proportion of non-infected donors may be classified as confirmed positive, using this as a stand-alone confirmatory test.

The non-Red Cross centers in REDS actually used a test that Bernie also referred to from Gene Labs, the diagnostic biotechnology Western Blot, which in addition to the p21E antigen has recombinant spiked proteins that allow you to more

accurately confirm envelope and type the donors. And this data was what was used in the analysis I'll show.

Just a comment -- this assay is no longer acceptable for use in blood donor screening because the company did not bring the assay in front of FDA.

So what we've seen with HTLV is in our first-time donors there is an apparent increase in prevalence. We've gone from around 30 per 100,000 up to close to 50 per 100,000, but this is actually artifactual, as I'll show you, limited to the Red Cross regions where basically it's probably attributable to false positive confirmatory data.

And similarly, incidence has apparently risen from less than one per 100,000 person years to over two per 100,000 person years. And here you can see this apparent shift up in prevalence, and you see sort of the bump right here, which is, again, when the confirmatory test problem became in play. And likewise, incidence at the same time -- all of a sudden we see this apparent dramatic -- you know, dramatic being a twofold increase in incidence at that point in time.

Now, as I indicated, the Red Cross regions were where they really moved to this less

specific confirmatory assay, and you can see that this change is actually limited to this region in red, where they have an apparent significant trend upwards. In this case, I think this is prevalence, whereas the non-Red Cross regions show this, you know, sort of stable, slightly declining trend.

So the point here is just to caution that until you really understand the confirmatory and screening test, what goes in determines what your analysis shows. And in this case, there is more data and more studies ongoing to really show that what has happened here is an artifact of the confirmatory test shift.

Just a little bit of data from the REDS group in terms of incidence from major parameters that REDS collects, such as incidence by gender, race, ethnicity, and then go on to more detailed analysis of incidence using a new strategy.

So just in terms of gender, we can see that for HIV males have slightly elevated incidence of HIV compared to females. A lot of these confidence intervals overlap. I think in REDS, for example, for HIV, we have about 30 or 35 incident cases. So the numerators, when we're talking incidence, are fairly low.

For HCV, interestingly, for a number of the marks that we'll talk about, HCV doesn't sort at all by the demographics. We really don't seem to be making much impact in underlying HCV prevalence or incidence, so we see here HCV is fairly constant between males and females.

HTLV, dramatically higher incidence in females than males. Most of our infections in our blood donor population are secondary transmissions of HTLV, mostly HTLV II, from male former IV use to female heterosexual partners. For HBV, incidence is much higher in males than females. So these things go both directions is one point.

Looking by race/ethnicity, you know, one interesting comment is, for example -- and we're talking HIV here, so I'll come to that other point in a moment. But for HIV, we see a significantly elevated HIV incidence rate in black non-Hispanics, slightly intermediate rates in Hispanics, and then low rates of around one per 100,000 person years in caucasians, and undetectable in Asians.

For HCV, again, fairly stable. This is a very small group, so a very wide confidence interval. But if you just look at your major donor populations -- black, Hispanics, and whites --

really no difference in HCV incidence across these different predominant groups.

For HBV, here was where I was going to comment that if you look at prevalence, HBV is much -- has a much higher prevalence in Asians, and yet in this country we can't detect secondary transmissions in the donor base within the Asian population. And most of the HBV transmissions that we're seeing are, again, clustered in the black non-Hispanic, probably related to parenteral exposure level.

And finally, HTLV -- again, the highest rates are in black non-Hispanics and Hispanics, presumably reflecting low-level parenteral exposures.

Okay. Now, to move on, though, the data I've presented is really the strongest, best data on incidence that we have in the donor base. But it's fairly limited to this one large study. There is fairly similar data beginning to come out of the Red Cross infectious disease data set, but it's limited because the incidence is so low we need these huge databases.

That database was around, what, about six or seven million donations over that period of time. It had to be, you know, compiled and

carefully evaluated in terms of culling out false positive results, and then analyzed very rigorously to capture person time for each donor and derive incidence rates. So it's a huge undertaking to stay on top of the incidence rates using those classical approaches, especially when your rates are as low as what we're dealing with in the donor pool.

In addition, those analyses were limited to repeat donors, and we really have a long-standing debate as to whether the donations by first-time donors are substantially higher risk and may have a higher incidence. And so, clearly, trying to get a handle on incidence rate in the first-time presenting donors would be useful.

And then, in addition, although I presented some data breaking these donors out by some demographics, as I told you, the number of incident cases was very small, in the range of 20 to 40 or so per virus. So to do further subgroup analyses is very difficult, given the low numerators.

So for this reason, for HIV -- and I think we could talk later about strategies for hepatitis C, but for HIV there has been a lot of work to develop a new approach to measure incidence in cross-sectional populations, a collaboration

really led in great part by Rob Jenssen and Glenn Satten at CDC, and with Sue Stramer and myself helping on the lab side.

And the approach is basically to take samples and take seropositive samples and reflex test them on a less sensitive assay. And we basically took a test that was an early generation viral lysate assay and purposely desensitized it or detuned it by running the assay at higher dilution and for reduced incubation times.

And by that, what we've been able to do is delay the detection of seroconversion by this less sensitive assay by an average of about four months. And we have, through a lot of work on seroconversion panels, defined the accurate confidence interval around that. And so what we can do is basically take samples from persons who were detected by the more sensitive testing strategies that we used, and reflex test them to find the people who are in this four-month window of early seroconversion.

And then, basically, you can multiply that rate of finding people in this window times three to derive an annual incidence rate. And this just shows that in schematic you test the population of samples, first-time blood donors, for example, or

any screen setting, reflex the confirmed positive samples to this less sensitive EIA, and identify the seroconverters -- the subset of the confirmed positives who had seroconverted within the prior four months.

And then doing a very simple calculation, you take the number of seroconverters and multiple that by 365 over 129 to annualize that, and then divide by essentially the number of subjects tested, and you derive an incidence rate. And there needs to be some slight adjustments if you have frequently sampled people.

One point I mentioned was the incidence in repeat versus first-time donors. And in a direct comparison in the REDS group, we derived incidence both by classic methods and by this detuned approach, and in both cases we got, by the observational incidence, an estimate of 2.6 by the detuned, 2.9 per 100,000 years, so very similar estimates. And then we compared that to an incidence in our first-time donors, and this just illustrates how the approach works.

So we had about 860,000 first-time donors in this sample population, 131 confirmed positive, 18 were in that transient early seroconversion window. And by simply running

through the formula, that yields an incidence in the first-time donors of 5.9 per 100,000 per year. So now we can contrast the incidence in our first-time donors with the incidence in our repeat donors and really conclude that the incidence in first-time donors is about two times that in our repeat donor population. So not that dramatically different.

There were a lot of concern or fears that the incidence in first-time donors would be much, much higher, partly because the prevalence is much higher, but the prevalence is much higher because you have all of the prevalent infections that haven't been culled out. So when you really have an approach like this to directly measure incidence in the two populations, we see that it's a really very small relative risk of first-time donors being window-phase type donors than repeat donors -- about 2.0-fold.

And you can then use -- you can derive a composite incidence rate by weighting that first-time and repeat donors, and these are the kind of numbers we're now using to estimate the residual risk based on understanding the infectious window, and to project the yield of new tests. So now we, for the first time, really have an appropriate

weighted incidence reflecting the first-time to repeat donor mix of incidence.

Okay. Now, the next analysis is really, I think, much more relevant to this discussion. Oh, I wanted to comment on one other point on the first-time/repeat business, which is that in REDS we've done a lot of work to look at the relative incidence among repeat donors, given, for example, the frequency that they've donated or how long have they been a donor.

And to make a long story short, there is no evidence that being a donor for any longer period of time, or donating any more frequently, further reduces your incidence. Once you're a repeat donor, your incidence seems to be really very stable for all viruses.

We've done a further analysis looking at the demographics using this same detuned strategy, and for this study John Aberle-Grasse and others at the Red Cross did a lot of work, and that's most of the data I'll present here now is crunched by John at Red Cross. So we had 1.7 million first-time donors in the Red Cross system during this approximately, I think a three- to four-year period of time.

Four hundred and twenty-seven of these were confirmed positive for HIV antibody, and when tested by this less-sensitive assay, 58 were recently-infected donors, which gave us an incidence in this first-time donor base of 9.6 per hundred thousand per year.

And if we look at incidence trends over time -- this is, I think, '93 through '96 -- we see a really very constant incidence in the Red Cross system, running just around 10 per 100,000. So no evidence that incidence is fluctuating or increasing, which would, for example, demonstrate some underlying increased heterosexual transmission that would be evident in the very low-risk donor pool. In contrast, we see a very stable, very low incidence.

If we look at our allogeneic donors versus our autologous donors, we have some evidence, actually, that the questionnaire does work because our autologous donors are individuals who come in to give blood for themselves, and they're not required to go through the risk factor questionnaire. And what we see is that autologous donors have about a twofold higher incidence rate than our allogeneic donors. No difference between volunteer and directed allogeneic donors. There is not enough

directed donors for this to have -- there is zero newly-infected directed donors.

But basically, certainly it doesn't support what's been debated, that directed donors may be higher risk because they're motivated to come in through some coercion, for example, from friends or family members. In fact, there is no evidence, I think, from this data or others that directed donors are riskier donors.

Okay. In terms of major demographic categorization, now, among these first-time, this large population of first-time donors where we can now get incidence using the less sensitive assay, we see that the incidence in male donors is around twice that of female donors, although the confidence intervals overlap, running around 12 versus seven per 100,000.

By age strata, the incidence in the male donors -- I'm sorry, the incidence is highest, about, again, two- to three-fold higher, in the middle-aged 25- to 45-year old subsets of our donors. The lowest rates are in the very young donors and the older donors.

Interestingly, the prevalence is about five-fold elevated in this intermediate group. So if you do things like an incidence to prevalence

ratio, there is actually a suggestion that incidence is beginning to take off in this younger age group, relative to the much lower prevalence in this group. So, clearly, there must be new infections beginning to occur here in order to drive the higher prevalence in this middle-aged grouping.

Now, one of the surprising and disturbing observations from this analysis was the dramatic difference in incidence by region of the country. The Red Cross divides their collection program up into six regions for these kinds of sort of demographic analyses.

And what we can see here is that the rates are really highest in the east coast regions in general, particularly in the southeast region where the incidence is 26 per 100,000 person years -- highly significantly elevated relative to other regions, with intermediate rates in the New England and mid-Atlantic coast regions, and then the lowest rates by far on the west coast and the central U.S.

So, really, much lower rates, less than two per 100,000 in the central and west U.S. blood donor populations, intermediate rates on the northeast coast, central Atlantic regions, and then much, much higher rates, really mirroring, I think, the bars that we saw from Rick Steketee from CDC.

Now, we were interested in that and further understanding that regional association. And to get deeper into that question, we went back to the REDS database, because the REDS database, although the numbers aren't as large, has the additional information, such as country of birth, race/ethnicity, and level of education.

So we wanted to see whether that apparent regional difference in incidence was actually a reflection of underlying demographic behavioral characteristics, to the extent we could get at those in the donor pool. And this just summarizes the same breakouts I just presented for the Red Cross national program -- much larger numbers -- for the REDS regions.

And the point here is you see the exact same thing -- a moderately elevated rate in males to females, the same kind of age clustering, with about twofold higher rates in the 25- to 45-year old group, and then down here the same regional differences with rates in the mid-Atlantic site of 12.2 per 100,000, which is about twice that of the other regions. So we had one region within REDS that's located in the mid-Atlantic region which had this evidence of a higher incidence in a particular collection region.

So we were able to, then, look at these other parameters, and then do a multivariate analysis to see if that regional collection site was really a fundamental property versus a surrogate for other underlying issues. And what we observed was really a reflection of what I presented earlier in the overall incidence analysis, that there was a much higher incidence in the black donor population. And this analysis -- about 50 per 100,000 incidence rate in this data set, compared to rates of about four per 100,000 Hispanic, and two per 100,000 in whites -- highly significant higher incidence in blacks.

Then, also, a highly significant higher incidence in individuals who only had a high school education. So around 16 per 100,000, which is around, you know, four or five times the rate in individuals who were still high school students, or individuals who had education beyond high school, running around four to five per 100,000. And no difference, no significant difference in terms of country of birth.

So then, Kevin Watanabe at WESTAT developed a multivariate analysis, which included all of these parameters -- gender, age, center, which is region of the country, race/ethnicity,

country of birth, history of blood transfusion, and level of education. And from that analysis, the only independent predictors of incidence were race/ethnicity, with blacks having a rate around -- with a relative risk of around 26 compared to an index group of whites.

And then, again, education -- only having a high school education, no advanced education, has about a three-fold independent relative risk for high incidence. So this is the insights we have at this point into sort of the underlying characteristics that are associated with higher incidence in the blood donor population.

But just to step back again and put this into perspective, we do know that the incidence is the primary driver in window phase, and this is a table that I think Sue Stramer may present later or present, you know, the core elements of it. But basically, what this table does is for each of the viruses it divides up the estimated risk really per year in the country. This is per 10 million screened donations. And divides them up according to whether they are due to window-phase risk versus other sources of risk.

And the bottom line, from my point here, is that really the window phase, which is

attributable to the incident infections, really is where the risk lies. But, again, these risks, these numbers are extraordinary low.

And I think we often fail to recognize and point out that we've driven down risk so dramatically, and that what we're dealing with in terms of these very, very low incidence rates that we're beginning to try to tease apart, but we're dealing with a consequent risk that's extraordinarily low. For example, for HIV, we only think that there may be no more than 15 infected donations per year that are being missed by these window-phase problems. For the other viruses, they are also quite low.

So that's the data I have to present. Thank you.

(Applause.)

DR. DAYTON: Thank you, Mike.

The next presentation will be from Toby Simon on prevalence and incidence of HIV, HBV, and HCV, in plasma donors.

DR. SIMON: Well, I'm pleased to be here and to be able to respond to the kind invitation from the agency to present data on behalf of the plasma industry. I do so as the Chairman of the Medical Directors Committee of the American Blood

Resources Association and a member of our ad hoc data gathering committee.

What we would like to present today is how the information and data that we have begun to accumulate relates to our Quality Plasma Program and how we are using it to help us in determining donor suitability and to reduce the risk or any safety issues involved with donation.

And as you can see, there is sort of a continuum of efforts that are made to increase and improve safety through the industry's efforts, beginning with that of trying to recruit donors from a safer population, to screen them appropriately, test, manage the inventory, additional testing, viral removal in an activation, all designed to give a safer product to patients.

The Quality Plasma Program, which is the overall program that includes our specific donor suitability effort, has a number of parts of it, and it is a program that has been imposed voluntarily by the industry upon itself to create standards that, in effect, are beyond that which has been mandated through regulation. And with, of course, the outset of safety reaching as close as possible to the zero risk.

It involves personnel training, HIV education, the use of community-based donors, a qualified donor standard, the abuse/drug abuse screening, the use of a national donor deferral registry, facility appearance standards, and a viral marker rate standard, which depends heavily on the data.

Now, of course, we are relying on the screening of the donor through questions that have been developed either through FDA regulations or guidance or by the standards of the industry, including the blood banking portion. And we use these questions to screen our donors.

The one difference between our centers and the volunteer blood donor centers is that we typically see our donors multiple times a month, as often as twice per week. And so that frequency may allow us to elicit information to determine donor suitability in a somewhat more timely fashion.

Secondly, before donation begins, and yearly for those who remain in our program, the donors have a physical examination and additional questions from either a physician or a physician substitute, the latter being licensed personnel, typically a nurse or an advanced emergency medical technician. And this process may also improve the

ability to determine donor suitability through the use of the questionnaire.

The specific programs that are different in plasma than they are in the blood banking sector, that are part of the QPP, I'll now discuss in some detail. The first is all of our donors initially and annually are subject to a drug screening procedure to determine if they have drugs in their system.

This is based on heroin or opiate testing, and any positive donors through this screening are rejected. These, of course, are documented. Any units would be destroyed that had been recently drawn. And, of course, it involves a system of proper sample identification. So the drug screening for opiates is an additional standard for donor suitability that we have introduced.

Next is the community-based donor standard to avoid donors who are transient. We have created the community-based donor standards, so for suitability we are also determining if the donor resides in that community, which we have arbitrarily set as a 125-mile radius, for some of our smaller towns that draw from large geographic areas.

The individual has to be lawfully in the United States. So for any of our centers that are

located near borders, the individual has to be able to show documentation that he or she has entered the United States lawfully, if they are not, indeed, a U.S. citizen with a driver's license or similar identification.

The individual must have permanent residence. If they have no permanent residence, they are rejected. And they cannot be incarcerated for more than three days within the past six months. So this assures that we'll use donors who are stable members of that community.

And finally, the other additional standard we have imposed is the use of the National Donor Deferral Registry. This is a national database utilized by the entire industry of individuals who will be permanently deferred from donating source plasma, if they are entered into the registry because of repeat reactive test results for hepatitis B surface antigen, antibody to hepatitis C, or antibody to HIV and HIV 1 antigen.

All new donors are screened against this registry and would not be considered suitable for donation if their names are there. We may be looking at the issue of using confirmed testing results rather than the repeatedly reactive in the future.

And then, finally, the qualified donor standard -- no individual is considered a suitable donor until they have appeared for a second time within a six-month period.

So to give you a little bit of detail on this, as you can see on your left, each individual, upon their first entrance into the donor center, is considered an applicant donor. The unit would be -- it would be screened, as we have shown. The unit would be drawn, but it would not be considered suitable for release, unless the individual returned a second time, which we've arbitrarily set within six months.

And then, if that individual completely qualifies on that occasion, they are considered a qualified donor, and all of their donations are releasable and considered suitable. This assures that we haven't missed any particular issues with the one-donor screening. So it gives us a second screening. It gives us a second set of test results to ensure there has been no test error.

And it also assures that the individual is the stable type of donor that we're interested in. We're interested in donors who will donate regularly with the program. So the individual who appears only once is not the type of donor that we

wish to consider suitable for our operations. So these are the additional standards for the qualified program.

Now, as a result of our data gathering efforts, we've begun to be able to test whether some of these measures are effective. And this looks at the viral marker rate comparisons, pre- and post-institution of our qualified donor standard. And using the data that we have available -- the pre-data is shown in the blue -- and this was before we began requiring confirmatory testing.

So with the introduction of confirmatory testing, we have adjusted the data to show the expected levels with confirmatory testing. And then, finally, in the green, to the right, we have been able to present the data post the qualified donor standard, with confirmatory testing.

So we've had substantial reductions in positivity for HIV, HBV, and HCV, the latter two most remarkably since instituting the qualified donor standard. And this message for us -- and hopefully for you -- is that the qualified donor standard, as an additional measure for donor suitability -- has been effective in reducing the viral marker rate.

An additional standard that really isn't donor suitability per se, but relates to this whole issue, is an inventory hold. There is a minimum of 60 days' period during which the units that have been donated are held for all qualified donor units. So the units are sent, released from the donor center, if the individual is considered suitable and is a qualified donor. They are shipped to the fractionator, who holds those units for 60 days, or more depending on the practices of that particular company.

If any of the units have a positive test, or any of those donors have a positive test subsequently during the 60 days, or there is post-donation information that indicates the donor, in retrospect, was not suitable, then the units are removed and not used for fractionation. And this is a measure that we're using to try to close the window period.

The next slide -- the overhead shows some of the data that we've been able to gather to show the effectiveness of the window period units by looking at those units which have been interdicted, and, therefore, not utilized. With HIV, it's close to a hundred percent. With HCV, it is less effective. And we've shown for both the current

serological testing and the currently being instituted PCR testing, which make the hold more effective, and then we have a residual with HBS.

So we are able to interdict a high proportion of the units, which can approximate a hundred percent with hepatitis B and HIV, and approximately 50 percent, if combined with PCR testing, for HCV. So that inventory hold has been successful.

The whole purpose, from our point of view, of collecting the data is to use it in a way to improve the safety of the final product. And we established a viral marker rate standard in 1991 for HIV and HBV, added it for HCV in 1993, lowered the rates for the previous two in 1993, and these maximum marker rates have been set for all repeat reactive donors.

Based on our most recent collection of data -- and the data that we'll be showing you was collected in 1997 during a four-month period -- represents the entire industry, all centers throughout the United States, and represents about four million donations. And now, using that data, which is now confirmed data, we will be establishing means plus two standard deviations, and now are

currently revising -- in the process of revising the viral marker rate.

So as we look at that mean and we take the outliers, and through the Quality Plasma Program require either relocation or closing of those centers that are outliers, we will gradually be moving the mean to lower levels and improving the safety of the product.

PCR testing is also a measure that will be used to improve testing, to improve safety as a test measure, and I believe at this point in time we're almost to a hundred percent in the American plasma industry and the institution of PCR testing for HCV, which closes that window from approximately 80-some days to 23 days. All the testing is being done under IND, and there is current exploration for the other two markers as well.

The data which we have gathered so far in our first effort is shown on this overhead, and the incident rates -- which were not on the overhead, but if you'd like to note them down -- for HIV, 63 per 100,000 person years; for HCV, 65 per 100,000 person years; and HBV, 247 per 100,000 person years, with the seroprevalence as shown.

And calculating for two different window periods -- the one that exists with the current

serologic testing and the one that will exist with the full institution of PCR testing -- we show for HIV a residual risk or window period risk for 10^6 donations of 1.47, with a current EIA down to 0.5 where the PCR is instituted. With HCV, with the EIA we're using the 82-day for second generation, 35.94, down to 3.32, when PCR is totally introduced, which we believe is imminent. And then for hepatitis B, using the EIA and a window period of 59 days, the current residual risk of 53.84.

This data gathering effort is ongoing and will continue for the entire industry. All of this data is based on qualified donors, since they are the only units that enter the pool that is actually used for fractionation. But we will be adding applicant donors to our data gathering efforts going forward. So going forward, we will have additional data collected, in 1998, for both applicants and qualified donors.

This data was presented by Barbee Whitaker at the AABB, and it is currently being written up for publication.

I wanted to add the fact that, as people are undoubtedly aware, that viral inactivation elimination is done as a last step. And I think it's important to discuss this, even though it's not

per se a donor suitability issue, because the fact that this is being used for all plasma derivatives does, I think, influence our decisionmaking as to where we go in additional donor suitability measures.

All products undergo either a viral inactivation or a viral removal procedure, in some cases with coagulation factors, two removal methods designed to inactivate HIV, HCV, and HBV. And the success of the viral inactivation measures has been summarized by Dr. Tabor in a presentation that he gave at the June BPAC meeting, and hopefully will be published in full soon. And it does indicate that even though we only theoretically bring the risk to zero, for all practical purposes there has been virtually no cases, or no known cases, since the viral inactivation has been completely instituted.

And this is since 1987 approximately for the coagulation factor concentrate, and since the one epidemic with the intravenous immunoglobulins was dealt with in the 1994 timeframe, and all of those products since then have been subject to a viral inactivation. There are no known cases since that time.

Now, this is not to imply that the donor suitability measures are not important, since we

all, I think, are believers in the layers of protection, and the need to have several layers in case there is a breakdown, as well as the fact that the viral load needs to be reduced to a minimum level with the log reduction procedures to be certain that we get as close to zero as possible.

But with this success record, I think one does need to ask, in that balance between safety and availability, which direction do we want to go, or how much further do we want to go in terms of either voluntary imposition of new safety measures by the industry itself or new regulatory guidance action by the FDA?

So our conclusion is that the initiatives have made plasma products safe and safer. The qualified donor standard, in particular, has reduced our seroprevalence rate. The inventory hold has permitted interdiction of a very high percentage of units in the window period. But the industry is committed to continuing these efforts, to continuing the data gathering measures, and to use them to continue to improve the donor panel with regard to viral marker rates and to increase safety and public confidence in the products.

Thank you.

(Applause.)

DR. DAYTON: We're now going to have about an hour's break for lunch. I guess if we -- it's about five past 12. So if we can show up here back at 1:00, we'll actually be back on schedule. And, of course, there will be opportunities for discussion and comments later in the afternoon. Thank you all.

(Whereupon, at 12:06 p.m., the proceedings in the foregoing matter went off the record for a lunch break.)

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

(1:04 p.m.)

DR. DAYTON: Welcome back to the afternoon session.

We're going to continue our section with a talk by Lynda Doll, after which there will be a question period. And I hope that those of you who have questions will also be interested in asking questions from our previous two speakers.

And now Lynda is going to talk on estimates of new blood donors, if eligibility criteria change.

DR. DOLL: Thank you, Andy.

Good afternoon, everyone. I'm going to try to -- this is going to be short, and I hope I can keep you awake after lunch.

I've been given three tasks this afternoon. The first task was to estimate the number of persons who engage in three HIV-related risk behaviors -- male to male sexual contact, injection drug use, and also receiving money or drugs for sex. That is, engaging in sex work. I will mention here that I was also asked to look at sex partners for these individuals, and I was unable to find the kind of data that I would need from the national surveys to be able to make these estimates.

My second task is of these persons who have engaged in misbehaviors, to estimate the number who may have abstained from these behaviors in some recent time period -- for example, one or five years. And then, finally -- and this is what I really am about doing -- is to arrive at an estimate of the number of potential new blood donors, if the exclusion criteria for blood donation were changed and these persons were then permitted to donate.

And how did I go about doing this? To arrive at these estimates, I first identified data on risk behaviors from large general population surveys with solid sampling methods and similar questionnaire items. And some of the surveys I utilized included several ways of the general social survey, the 1996 national household survey of drug abuse, the national survey of adolescent males, the national health and social life survey, and the national AIDS behavioral survey.

I utilized these general population surveys because I thought these data would better approximate the kind of risk behaviors that blood donors might engage in.

Next, I also then compared the various findings from across the various surveys, and then established, where possible, ranges for prevalence

rates for the risk behaviors for several time periods -- ever, one year, and five years -- and also tried to approximate since 1977.

Then, using 1996 Census data, I translated these rates into actual numbers of persons who might be engaging in the risk behaviors and then who also might abstain from these behaviors more recently.

And then, finally, assuming a five percent rate of blood donation, I calculated the number of abstainers who might attempt to donate blood. And what I want to do now is to review these estimates for you, and I will end by giving you some of the limitations of these data and of the data sources, which are, by the way, many.

Okay. These are the 1996 population Census estimates that I worked with. In 1996, there were approximately 96 million men in the United States and around 103 million women in the United States. So we're going to start, first of all, with the estimates of the number of MSMs.

Now, again, my goal in this was to arrive at the number of MSMs who had same sex contact but abstained from sexual contact with men in the last five years or the last one year. This

group of abstainers then might be eligible to donate blood.

I was asked also to look at one point at two-year time period, but a two-year time period is not used on most sex surveys. So you won't see a two-year time period here.

I first found estimates of the number of men who report engaging in sex with another man for three periods -- since age 18, which in this case I'm using to approximate since 1977, in the last five years, and the last one year. And sources for these data are listed across the bottom, and they are the general social survey, the national AIDS behavioral survey, and the national health and social life survey.

And together, these surveys provide a fairly consistent and representative estimate, I think, of same sex contact in the United States.

I split the data into two age groups. The data at the top of the slide are for 18- to 49-year olds, and they come from six waves of the general social survey and the national AIDS behavioral survey, from 1988 through 1994. And then on the bottom you're going to see estimates for men ages 50 to 59, and this comes from, again, the national health and social life survey.

You will note that the estimates of men ages 14 to 19 reporting same sex contact decreased with age, ranging from just over five percent since age 18 to about 2.6 percent contact in the last year. And, importantly, notice also that the rates in the central cities of the 12 largest SMSAs are much higher than are those for the general population overall.

If you look at the bottom figures, the rates for men ages 50 to 59 are much lower than for younger men, ranging from approximately four percent since age 18 to over one percent in the last year.

All right. Now what I did was to estimate the number of men who abstained in the last year, for the last five years as well as the last year. And among the men in the younger age group, which is the top line, I estimated that 25 percent of men had abstained in the last five years. And for men ages 50 and over, I estimated that 40 percent had abstained in the last five years. Together, these figures suggest that approximately 1,385,000 MSMs have abstained in the last five years.

Then, moving on to the one-year abstention, looking at the second category, the last -- the column on this side, I notice that 51 percent

of the men ages 17 to 49, and 67 percent for men ages 50 and over, had abstained in the last year. So we arrive at a figure of roughly 2,638,300 men abstained in the last year, but had reported having sex with another man since 18.

And now we're looking primarily here at the number donating category. So among those who abstained in these two time periods, the number of men who might show up at the blood center was of interest to us. And I estimated that five percent would donate in a year. This is the approximate estimate of the percentage of the general population who currently donate on a yearly basis.

Then we arrive at the following figures. Among men who abstained for the last five years, approximately 70,000 might donate blood if the criteria change. And among men who abstained in the last year, which is the last column on this side, approximately 132,000 might donate.

Now, the next slides are much easier to understand, and the next set of slides are for injection drug users. And to estimate drug use, what I used was data from the national household survey of drug abuse and the national survey of adolescent males. Note that in the case of these surveys, I have used ranges of prevalence rates, as

different surveys show quite different rates, depending upon the methods of data collection that were used.

These surveys show that between 1.2 percent and 5.2 percent of persons report ever injecting drugs. Far fewer persons, from .1 percent to .8 percent, of persons report such use in the last year. Data are not available for a two-year time period or a five-year time period because, again, these questions have not been asked on these surveys.

This slide shows the number who actually abstained, of those who have ever injected. I estimate that between 2.4 million and 10.4 million persons have ever injected drugs, and that those between 2.3 million and 8.8 million abstained in the last year.

And then the final figure -- the estimates of the numbers of IDUs who might donate. Assuming, again, that five percent of those abstainers in the last year might donate blood, this means that between 110,000 and 440,000 former injection drug users might potentially come to the blood donation centers to donate.

The final category that I'm going to show you is for the numbers of persons who receive

money or drugs for sex. In this case, I'm only able to provide data for women, primarily because the survey items do not differentiate between individuals receiving and giving money for sex, money or drugs for sex. And because of this confounding, I think it's impossible to look at figures for men.

On the other hand, though the data on women are also confounded by this, I think we can assume that far fewer women give men money for sex. So, therefore, I am providing you with these data.

For estimates -- by the way, some surveys actually do show that women give money or drugs to men for sex, so it's not that unusual. For estimates of sex among women, we used data from the national household survey of drug abuse and the national health and social life survey. And only one survey showed lifetime rates, and the data showed that 1.9 percent of the women reported engaging in this behavior, with the rates decreasing to between .2 percent and .5 percent in the last year. Again, data are not available for two- and five-year time periods.

Okay. Now, of those women who have ever engaged, which is roughly 1,968,000, those who have received money or sex for drugs, we estimate that

approximately 310,807 have engaged in it in the last year, which means roughly 1.6 million women have abstained from this behavior in the last year.

And assuming a five percent donation rate, I am calculating that roughly 82,900 women might potentially donate who have at one point engaged in this behavior but have abstained in the last year.

So what do the data look like all together? Here are the final figures for the three population groups. If the blood donation criteria require the donors not have engaged in specific risk behaviors for only the last year, 132,000 men who have sex with men, between 110,000 and 440,000 injection drug users, and roughly 83,000 female sex workers might potentially donate blood.

I also want to note here, however, that it's important to realize that some unknown number of these individuals actually are currently donating blood, despite the fact that they have been told they cannot. And I believe Alan Williams is going to give some of these figures or talk a bit about these kind of data from the REDS data later on.

It's really, really important that I talk about the limitations of these data. First of all, it's very hard to arrive at reliable estimates

of the size of these populations, particularly injection drug users and persons who have received money or drugs for sex. My estimates for at least these populations probably undercount quite substantially the actual prevalence of these risk behaviors.

In part, this is because surveys actually do not sample in settings such as jails and other institutional settings, where individuals who engage in these behaviors are often found. The surveys also rely entirely upon self-report data -- well, almost entirely -- and participants may be uncomfortable in disclosing this risk, particularly recent risk.

Also, it's very hard to extrapolate these estimates across the different surveys because the various surveys use different items, different data collection methods, and so on and so forth.

And again, there's a bullet that was actually left off of this slide for some reason, but I think it's an extremely important one. And that is that I've used a five percent estimate of the individuals who actually might donate blood, this being the rate of general population donation.

This may actually quite overestimate the number of these individuals who might suddenly show

up to donate blood when they have been told for years that they should not. And I think this is a very important point to make, but this is probably the worst case scenario that I'm giving you.

Also, again I want to estimate -- mention to you that the estimates of sex worker are particularly problematic. The items on most of the surveys -- in fact, all of the surveys that we've been looking at -- do not differentiate between receiving and giving money for drugs, and, therefore, there are no useful data available on men, and the data for women are confounded, though I think not -- I think the bias is not very, very, very strong.

And finally, just a couple of points of interpretation that I wanted to make as you're thinking about the possibilities of changing the criteria. First of all, I think it's very important to remember that reports of risk behaviors are usually much greater in urban areas. And I showed some data for that on MSMs.

And finally -- and this has been found repeatedly over the years in most of the surveys -- and that is that few persons over 50 report recent risk behaviors.

Thank you.

(Applause.)

DR. DAYTON: At this point, I'd like to see if anyone is interested in asking questions of any of the three previous speakers. We've allocated a little time now for a brief question period. If anybody does have any particular questions they'd like to ask, please come to the microphone or indicate.

DR. BIANCO: I wanted to ask Mike Busch, just for the benefit of all of us mortals, if he could relate --

(Laughter.)

-- person years to real numbers, as he compares first-time donors and repeat donors, so that we have a sense of how many donors really walk in.

DR. BUSCH: Well, I mean, the concept of person time is -- in a sense, for the donor pool you could imagine that if you talk about four per 100,000 person years, that would, in essence, be as if you had 100,000 individuals that were donating, you know, consistently over one full year, you would have four seroconversions in that year period.

And again, to translate that into risk, you have to understand that those seroconverters are actually only infectious and antibody negative for a

very brief week or two. So only for that fraction of a year would they be contributing a risk of a seronegative unit that we then use. So you multiply the person time incidence times the window to get --

DR. BIANCO: And how many people do they represent over the --

DR. BUSCH: Celso is asking how many individual people are represented in those analyses. Within the REDS analysis, for example, I think for repeat donors we're probably talking about one and a half million individuals who gave over periods of this four- or five-year followup time.

DR. BIANCO: And how many seroconversions?

DR. BUSCH: And the total number of seroconverters -- for example, for HIV, I think it's about -- probably about 30. For some of the other viruses it's -- you know, for HCV, perhaps it's something more on the order of 50.

DR. DAYTON: Are there any other questions or comments at this point?

Okay. Well, this catches us up a little time. Let's get moving.

The next talk is going to be by Ken Clark, who is talking on risk factors in blood donors positive for HIV.

DR. CLARK: I'd like to thank the FDA for inviting me to talk today. My talk is on trends in HIV prevalence and risk factors and risk behaviors among U.S. blood donors. I'll be presenting data from the CDC blood donor study that is now in its eleventh year of data collection.

Since 1985, all blood donations in the United States have been screened for antibodies to the HIV virus. Although the current screening tests are extremely effective, there still remains a small but real and quantifiable risk of transmission of HIV infection through blood transfusions. Therefore, in order to optimize protection of the blood supply, blood collection centers use a combination of screening strategies.

In addition to the excellent laboratory tests, the blood centers also use pre-donation deferral questions. All potential donors are asked to answer both written and oral questions about risk behaviors that would put them at increased risk for acquiring HIV infection.

Although these pre-donation questions should eliminate most of those persons with risk behaviors from the donor population, these pre-donation questions are only effective if the

potential donors are aware of both their own risks and those of their partners.

The objectives of this study have been to describe the annual HIV seroprevalence among blood donors in the United States between 1988 and 1997, and, furthermore, to assess the prevalence of risk behaviors among the positive donors.

This ongoing study is now taking place at 15 blood centers in the United States located in multiple metropolitan areas chosen partly because of geographic diversity and partly because of the high HIV prevalence in those respective communities. We have been collecting data continuously between 1988 and the current time, and have analyzed it through the end of 1997, on the total number of all donations, all non-autologous donations at these centers, and on the number of those donations that test positive for HIV antibodies.

All persons who test positive are eligible for enrollment in the study if they are 18 years of age or older and have not previously enrolled. All of these positive persons are offered enrollment after standard HIV donation and counseling. Trained interviewers administer standardized questionnaires in which they ask these positive donors about their risk behaviors. Those

donors are then placed into a hierarchy of risk categories that is based on a system that the CDC uses for AIDS case surveillance.

This hierarchy begins with the category men who have had sex with men, followed by injection drug users. Then, there is the category of persons having heterosexual contact with men who have had sex with men, with injection drug users, or those who have had heterosexual contact with hemophiliacs or persons with coagulation disorders. And finally, with persons infected with HIV.

Those persons who are not placed into one of these risk categories are then placed in the no reporting risk group. These persons are then reinterviewed at a later time in order to increase the chances of identifying a risk category.

Since the beginning of the study in 1988, we have looked at over 23 million non-autologous donations. Of these, 3,291 were positive for HIV antibodies, for an overall seroprevalence of 14.1 per 100,000 donations. Of these positive donors, 1,997, or nearly 2,000, have agreed to enroll in our study. The remaining 39 percent either refused enrollment or were lost to followup.

Now let's look at some of the data from this study. This chart shows the prevalence from

1988 through 1997 for men in the top blue line, for women in the bottom yellow line, and for the combined men and women category in the center green line. We can see that in 1988, for the combined group, the overall prevalence was about 23 per 100,000 units, while at the end of 1997 it was about nine per 100,000 units.

More dramatically, we see that in 1988 the prevalence for men was 31 per 100,000 units, and, in 1997, it is about 10 per 100,000 units, or a decrease in the prevalence over this time period by two-thirds. For women, the prevalence in 1988 was 12 per 100,000, while currently it is about eight per 100,000. So we have a decrease over the same period in prevalence by about one-third.

We can also look at the prevalence by risk categories. Here we see data for men alone. The way we calculate this prevalence is we take the total number of men who are found in each of the major exposure categories or risk groups and divide that by the total number of men who donated blood in that same time period. For example, in 1988, there were 225 men who reported having sex with another man. These are of the HIV positives, out of a total number of 2,225,000 donations, for a prevalence at that period of 10 per 100,000 donations.

We can see that the prevalence has changed from 10 in 1988 to its current level of a little over two per 100,000 for the MSM category.

For injection drug users and persons in the blue line, and for heterosexual contact risk group persons in the yellow line, the prevalence has always been fairly low by comparison. The green line shows those persons in the no reported risk group that has declined slightly over time.

We can look at the same prevalence by exposure categories for women. And although there appears to be a slight decrease over the time period of this study, statistical tests for trends actually shows that there is no such decrease. The bottom line is the prevalence of injecting drug users among women, which has always been very low. And, in fact, since 1994, we have only had one positive woman who has admitted injecting drug use as a risk factor.

This set of stacked bar charts looks at the proportion of seropositive donors in each of the categories, in the first and last years of the study for both men and women. We can see for men between 1988 and 1997 the relative proportion of persons in the MSM group has decreased, as has the relative

proportion of persons in the injecting drug use category.

For women, we see a similar change in the injecting drug use category, and a slight decrease in the heterosexual risk category. However, for both men and women, we see an increase in the number or the proportion of persons who report no reported risk, or for which we do not find a reported risk.

We can also look at the 1997 data alone in these two pie charts in a more quantified fashion. We can see that in 1997, among men, between the categories MSM and injecting drug use, a total of 43 percent of the persons fall. What is amazing to me about this percentage is that of these 43 percent of the men who are HIV positive in these two categories, every one of them in their original pre-donation questionnaire failed to acknowledge a risk factor.

For women, we see that the major identified group is heterosexual contact. For women, over half of the persons, though, are in a no reported risk group. And 43 percent of those -- of men are in the no reported risk group.

We know from our study that the vast majority of these persons in the no reported risk

group do acknowledge unprotected sex with multiple partners. Therefore, we must assume that at least a significant number of them could actually go in the heterosexual contact group. However, for them to be placed into those categories, not only did they have to know their own risk factors, they must also know the risk factors of their partners. And this information is very difficult to obtain.

We can also look at the major risk categories in relationship to time since they last engaged in their risk behavior. On this slide, we see that data for men who have had sex with men in two representative years -- in 1990 and in 1997 -- we see that the vast majority of the persons in those two years engaged in their risk behavior within one year of donation. Only a minority stated that their risk behavior was more than one year before donation.

The next slide shows similar data for injecting drug users. However, in contrast to the MSM group, we see that in these same two representative years, a hundred percent of those persons stated that they engaged in their risk behavior more than one year before donation.

We also looked at this data for persons who have sex with others in exchange for either

money or drugs, but the number of persons in this group was extremely small. And, in fact, in 1997, there were no such persons.

We can make a number of summary statements from this study. First, as we have seen, between 1988 and 1997, the overall HIV seroprevalence has been declining for both men and women and for all of the identified risk categories. However, the proportion of donors with no reported risk has increased over this same time period.

Also, as we have seen, particularly in the injecting drug users and the MSM groups, people aware of their risks continue to donate. And finally, many donors may be unaware of their risk, partly because they do not know the risk behaviors of their partners.

And finally, I would just like to thank our collaborators at the American Red Cross and the CDC HIV blood study group, for collaboration in this study.

Thank you.

(Applause.)

DR. DAYTON: Considering that we're well ahead of schedule, if anybody would like to ask some questions, we can have -- Jay?

DR. EPSTEIN: Dr. Clark, on the study of prevalence in donors, I think you showed an uptake in both males and females from '96 to '97. Is that statistically significant?

DR. CLARK: Well, the question of significance, I have to qualify it. I'm sure because of the large number of persons in the denominator, statistically it would be significant. But whether it means anything or not, I can't answer that. I think that as soon as we finish collecting our 1988 data, we're going to need to continue to run the analysis and see if that trend continues.

Right now, I cannot tell you whether it really means anything. But I'm sure statistically it is significant, just because of the number of people in the study.

DR. DAYTON: Thanks.

DR. IAN WILLIAMS: Ian Williams, CDC. It's a very nice study. I had a question. As you looked over time, did you see changes in other markers, such as age, race, ethnicity, any marker -- socioeconomic status -- that concurs with these changes in risk pattern? Or was the population relatively stable from year to year in terms of their baseline demographics?

DR. CLARK: Well, I would have to say that I don't know the answers to those questions. I am at a little bit of a disadvantage in that I'm very new to this study. I've just joined the study. Those data are in our data set, but I have not had time to do an analysis on all of those prior to this talk.

DR. BUSCH: It was interesting to see that among the male sex male group that the risk behavior within the prior year was fairly substantial. I think it was about half had continued to engage in it in the past year and yet donated. Whereas, within the IDU group, there was no recent behavior.

And I guess one of the thoughts that is I think, you know, from a sort of scientific perspective arguing for revision of the criteria, is to actually focus people's attention on recent behavior because they are continuing to -- they are basically sort of putting blinders on.

They are saying that the current policies don't make sense, these historical risk behaviors. And so they are deferred no matter what, and so I think perhaps some individuals, were we to change the policies to focus on behaviors in the

past year, they might attend to those recommendations more so than they are now.

Is there any -- I'm just trying to think of, you know, why would the injection drug users, you know, really -- persons who had injected in the past, they seem to be aware of the fact that the recent behavior is much more important than the remote behavior, whereas the male sex male group don't.

DR. CLARK: Mike, I'm afraid I can't give you a definite answer on why that is happening, but we do have to acknowledge that it's a very small number of persons who are in those groups. If we look at the total population in 1997 of men who were positive, it's only 77. And I think that we would need to do further studies to answer your question.

DR. BIANCO: Celso Bianco, New York Blood Center. Ken, you did a very fast -- a beautiful analysis of these data. There is another piece that I see in the data that would be very important for the type of issues we are dealing with. There's the perception of risk by these donors. Those donors -- they went through the system. They answered the questions, they donated, and they were positive. And those questions are asked in the questionnaires.

And at least in the portion that I see as one of the participants of the study is that the majority -- the vast majority of them had no idea that they were doing something wrong, that they missed the boat. So that they really missed the questions. The questions missed those -- all of those individuals that you analyzed.

DR. CLARK: Thank you for your comments.

DR. DAYTON: Well, why don't we move along. We're still ahead of schedule.

The next talk will be by Simone Glynn on risk factors in blood donors positive for HCV.

DR. GLYNN: Hi. Let me see if I can get my first slide.

Okay. Well, good afternoon. I'd like to present the results of a case control study that was done to evaluate the risk factors for HCV infection in a population of U.S. blood donors.

This was a study conducted by the donor epidemiology -- by the retrovirus epidemiology donor study group. And, as Mike indicated before, we have five blood centers participating in REDS, in different geographical locations. We have a coordinating center, and the study is being sponsored by NHLBI.

Well, the prevalence of HCV has been reported to be about 0.36 percent in U.S. blood donors. However, the prevalence of risk factors that are commonly thought to be associated with HCV infection in the general population have not been as well defined among the blood donors.

There have been very few case control studies done to evaluate risk factors associated with HCV infection in blood donors. I think one was done in England and one was done in Australia. They both found that there was -- that injection drug use was a very common risk factor among cases.

There was another study done in the U.S., and that study actually showed that the most prevalent risk factor was intranasal cocaine use. It was present among 68 percent of their cases, while only, I think, 42 percent of the cases had injection drug use. So whether inhalation of drugs is an HCV risk factor, independent of injection drug use, certainly merits further consideration.

So as I mentioned, we performed a matched case control study to evaluate HCV risk factors, and to do that we first identified all of the confirmed HCV cases from the five REDS centers between 1994 and 1995. And we found 2,316 HCV positive.

We then matched a similar number of seronegative controls to those cases, and they were matched by age, sex, race/ethnicity, center, and first-time versus repeat status.

Okay. We then sent a questionnaire to all of these potential cases and controls. This was a self-administered questionnaire that was then sent back in an anonymous fashion to the coordinating center where the data was compiled. And then we analyzed the data using conditional logistic regression to take into account the matched design of the analysis. And we will be reporting unadjusted odds ratios, odds ratios adjusted for injection drug use, and, finally, a final multivariate -- a multivariable model.

First, I want to show you the response rates that we obtained. For the HCV cases, 758 returned the questionnaire, so that represented 33 percent of the original number. And for the controls, 1,039 responded, for a response rate of 45 percent among the controls.

And response rate was also differential, depending on the demographic categories. So as you can see, if you go down this slide here, as you -- if you are an older donor, if you are female, if you are white or Asian, if you had given an apheresis

blood donation, or if you were a repeat donor, you were more likely to return your questionnaire than your counterpart.

Okay. We then evaluated whether cases and controls were similar or not, in terms of their demographic characteristics. And not really surprisingly we found that the matched factors, which were age, sex, race/ethnicity, blood center, and first-time versus repeat status, were really pretty similar between cases and controls.

We also found that donation date, type of blood donation, marital status, and the birthplace were also not statistically different between cases and controls. However, we found that the HCV cases were more likely to have a lower level of education, and they were also more likely to have a higher alcohol consumption than controls.

The first category, in terms of risk factors, are the drug-related risk factors. And the most important one of those was injection drug use, where 51 percent of cases reported injecting drug ever in the past, compared to only one percent of controls. So that gave us an odds ratio, and, again, that was adjusted for the matched design of 134.5.

Now, if we look at what happened among the injection drug users, we found that actually the cases who injected drugs were about three times more likely than the controls to have used a used needle while injecting drugs.

Living with an injection drug user and inhaling drugs were also risk factors, even after adjustment for injection drug use. And I'd like to point out here that when you look at the unadjusted analysis for these two factors, you see quite high odds ratios. And then, as you can see in the analysis adjusted for injection drug use, the odds ratio dropped rather dramatically.

So, for example, for inhalation of drugs, you go from an odds ratio of nine to an odds ratio of 2.2. So that shows that there was some significant confounding by injection drug use.

Looking at the transfusion and medical risk factors, we found that having had a transfusion in the past was a major risk factor in that category. It was interesting, though, that this association was present only among non-injection drug users. And you can see here the odds ratio has been stratified and is significantly higher only in the non-injection drug user with a level of 8.3.

We also found that immunoglobulin injection, having had a bloody needlestick injury in the past, and even having had surgery and having had sutures, although to a much weaker extent, were also associated with HCV infection, even after adjustment for injection drug use.

The affect of injection drug use -- as you see, between the unadjusted and the adjusted, the odds ratio is certainly not as much in that category as in the previous one.

Okay. Going on to other miscellaneous or parenteral exposures, we found that having been in jail for more than three days was, again, a significant risk factor. Again, quite confounded by injection drug use, but the odds ratio still remained highly significant at five after adjustment for injection drug use.

Being tattooed -- oh, yeah, having pierced ears or body parts, and being part of a bloody religious ritual, were also all significantly associated with HCV infection. That doesn't sound very appetizing, does it?

(Laughter.)

Okay. The next ones, which are shared toothbrush or razor, this was essentially not significant after adjustment with injection drug

use. And having had acupuncture was not significantly associated either.

Okay. Going on to sexual exposures, we found that the major variable out of all of those was having had sex with an injection drug user. And there we found that the odds ratio unadjusted was about 42, and, as you can see, it dropped again, but still very high after adjustment with injection drug use, so that cases were about, what, 10 times more likely to report having had sex with an injection drug user than controls.

We also found that having had sex with a transfusion recipient, sex with a hepatitis case, and having had an STD were all significantly associated.

You might note that having received money for sex was not significantly associated with HCV infection after adjustment for injection drug use.

Okay. We then did a study which was stratified by gender, and we tried to evaluate whether the number of lifetime partners was an important risk factor. So when we looked at men and the number of lifetime female partners, we found in the unadjusted analysis that there was a nice trend

with odds ratio going from one to about seven, as the number of lifetime female partners increased.

However, actual adjustment for injection drug use -- we found that that trend became much weaker as you can see here.

In women, looking at the number of lifetime male partners, we found that the odds ratio increased rather dramatically, again, as the number of partners increased. So even after adjustment for injection drug use, the alteration went from one to about nine.

I always think that maybe the difference between the two analyses is in support of the fact that probably in HCV the transmission from male to females is probably easier than it is from female to males.

We went on to build a final multivariable model, and to do that we considered all of the variables that were significantly associated with HCV infection, and even after adjustment for injection drug use. So these were quite a few variables, as you can imagine. But we did a combination of backward and forward stepwise modeling procedures and ended up with eight variables in this final multivariable model.

The three major ones were injection drug use, with an odds ratio of about 50; transfusion in non-injection user only, with an odds ratio of about 11; and the other big one was having had sex with an injection drug user, with an odds ratio of six.

We also found five other weaker risk factors, and these were incarceration, religious scarification, having had a blood needlestick injury, pierced ears or body parts, and immunoglobulin injection daily -- made the significance level, which was .05.

So then we tried to look at our population of cases and see how many we could explain by the combination of having at least one or more of those AIDS risk factors. And we started with the risk factor that had the highest association that we found in our study, and that was injection drug use. So that explained that 51 percent of our cases, as I said before.

We then went on and found out that there were about 16 percent more cases that had had blood transfusions but did not have injection drug use. Another six percent of cases had had sex with IDU, and not the previous two factors, so essentially the first three risk factors explain about 74 percent of our cases.

We then found that the five weaker risk factors explain an additional 16 percent, so that only 10 percent of our cases did not have any of those AIDS risk factors.

So, in conclusion, injection drug use was the strongest and the most common HCV risk factor in this population of U.S. blood donors. We also found that sex with an injection drug user and having had a previous blood transfusion, but only among non-injection drug users, were significant risk factors. And the weaker risk factors we found, again, were incarceration, religious scarification, having had a blood needlestick injury, body piercing, and immunoglobulin injection.

Now, these weaker risk factors should be interpreted with caution, considering possible response bias. Then, although nasal inhalation of drugs was a risk factor in both the univariable and the bivariable analysis that I've shown you before, it just did not stay significant in the model after we adjusted for other risk factors.

So we hope that these data may be useful in designing modifications to the current donor screening procedures. Thank you.

(Applause.)

DR. DAYTON: We're still running ahead of time, so if anybody would like to ask Simone questions, we'd be very happy to have some questions from the floor.

DR. IAN WILLIAMS: Ian Williams, CDC. It was a very intriguing study. I guess I'm just trying to resolve sort of what you showed versus our data that looks at people who actually have acute hepatitis C, where we rarely see people that are tattooing, body piercing, inhaling, we just never see those as risk factors. Less than one percent of our acute cases actually report those risk factors.

So I guess what I'm trying to ask is: what can you do to convince me that those people in your study who deny injection drug use aren't actually truth challenged? Because it seems like jail time, more than 50 sex partners, are actually probably good proxies for people who might be injectors and won't admit it. What can you do to tell me that those people are telling you the truth?

DR. GLYNN: Well, we tried to get at that by doing all of these adjustments for injection drug use, to try to take into account --

DR. IAN WILLIAMS: My question is: among those people who don't inject, who deny injecting --

DR. GLYNN: Who deny injection, and then why is it so elevated compared to your findings? Do you mean the percentage?

DR. IAN WILLIAMS: The question is, is how do you know those people who deny injecting aren't lying to you?

DR. GLYNN: Oh. I did not know that.

DR. IAN WILLIAMS: Have you looked at -- well, I mean, I think it's an important point because your rates are relatively modest. And if you had just a handful of people who, say, have ever been in jail are actually injectors, that could cause your model to be different.

I guess, have you looked at, say, age, race, sex, characteristics among those who deny injection versus those who admit to injection, to see do they look exactly the same as those people? Are they somehow different in terms of baseline characteristics?

DR. GLYNN: Yeah. I haven't looked at that separately. As you know, this study was matched for those factors.

DR. IAN WILLIAMS: No, no. I'm talking --

DR. GLYNN: So it's difficult to look at.

DR. IAN WILLIAMS: No. I'm just talking among your cases.

DR. GLYNN: This was --

DR. IAN WILLIAMS: So among your cases, if you look at those who inject versus those who don't inject -- high-risk factors -- do you see the same distribution of age, race, sex, among those who inject versus those who don't inject? Or do they look like similar groups?

DR. GLYNN: Yeah. I do not know that, but I will -- we will look into this.

DR. IAN WILLIAMS: All right. Thanks.

DR. DAYTON: Well, if there are no more questions, we can move along.

The next talk is going to be from George Schreiber on risk factors for HTLV positive donors.

DR. SCHREIBER: I think you'll see a fair number of similarities between this presentation on HTLV and the one you just saw on HCV, in that some of the analytical procedures and the risk factors looked at are the same.

Here's a study that has been done by REDS and has been published, so that the first part of it is available to anybody. What I've tried to do is break this presentation down into two parts. One is risk factors, and then there was a request to

look at prevalence figures for HTLV within the REDS donor base. So those are tacked on to the end, and if we have time I'll run through some of those.

This is REDS, funded by NHLBI. The same five centers that were on the last slide are still on this one. This is a frequency matched case control study of HTLV confirmed positive blood donors. These individuals were identified prior to the start of REDS and from 1991 through 1992. And they were matched with seronegative controls, which were randomly selected from donation databases at each center.

These controls were frequency matched to the cases by age at interview -- we used five-year strata -- sex, race/ethnicity, type of donation, whether it was community or autologous or directed, because we felt that they might have an important role in the transmission. And for HTLV, it was typed by peptide, Coulter, or PCR.

We had 965 eligible HTLV donors who were contacted or identified, and we had an enrollment rate of about 57 percent. We contacted 1,677 seronegative controls, and we had almost 800 -- about 48 percent -- enrolled. We had unmatched cases, 11, and controls, 86, and then we had a few

untypable seropositives, which were excluded from the analysis.

The untyped cases and controls come from the way we did the matching. What we did is when we identified a case, to try to expedite the enrollment of the controls, we would issue three controls for each case. And if the control didn't enroll, then if they were available and were a match for the next set of controls, for cases, then they were enrolled.

Very often what happened is on the questionnaires of the donor enrollment the individuals had the wrong ethnicity or they had the wrong age. So then they would be matched to the wrong groups. So we had some people that were leftover and couldn't be matched.

And then in certain groups, like the Asian groups, it was very difficult to match because of the few donors. So there are a couple of those that were non-matchable. And if you break this down, we had 149 HTLV cases, 381 HTLV II cases, so you can see it's roughly 70 percent of HTLV II in the donor population. And then we had the 713 controls, which are included in the analysis here.

We did a host of risk factors -- sociodemographic, education, parents' region of birth, breast-fed, living overseas, parenteral, we

had blood transfusion, tattooing, injection drug use, sharing needles and syringes, and stuck or cut with blood-contaminated instruments.

On the sexual side, we had lifetime sex partners, sex partners, or parents or grandparents of a sex partner from an HTLV endemic area, sex with an injection drug user, sex with or as a prostitute. We tried to evaluate condom use, homosexuality or bisexuality, history of STD, sex partner who ever had a transfusion, and we also looked at, I think for the first time in one of these studies, pregnancy history, including abortion. And, in fact, that turns out to be an interesting factor which you'll see later on.

We used the same type of conditional logistic regression, and what you'll see here are both bivariate and multivariable presentations of the data.

I'll have to come around a little so I can see this. This is comparing just the cases and controls for HTLV I. And as you can see, because of the control matching, you get a fairly good distribution. And the distribution of the males and females is about the same for the two viruses.

For HTLV I, you can see that there is a higher percentage of non-whites than for HTLV II.

And in HTLV II, we have a much higher percentage of Hispanics as cases than we do for HTLV I.

In this slide, you can see that there is a shift between HTLV I and HTLV II in the age distribution. And you can see that the HTLV II are a younger group than the HTLV I cases. Again, the parallel, since they're matched by age, race, sex, and the other factors, the controls mirror the cases very well.

The other thing is that you can see that there is a difference between the degree of autologous and non-autologous between the HTLV I's and the HTLV II's. This might, in part, be reflected by the difference in the age distribution.

Education for -- now, this looks at the odds ratios for the HTLV I infection. And as you can see, that the least educated group has the highest odds ratio. So that the risk of HTLV I infection decreases as the education level increases.

Breast-fed -- there's about a risk factor of two, odds ratio of two, so those that were breast-fed are at higher risk of HTLV I than those who were not breast-fed.

Those that were stuck with a sharp instrument which had someone else's blood on it also

had an elevated risk factor, also on the order of about two.

Now, if you look at transfusion, again, you can see that transfusion was a significant risk factor for HTLV I, almost by a factor of five. Tattooing -- again, on the bivariate analysis -- again was a significant risk factor, for those who were tattooed had about three times the risk of HTLV infection than those who were not tattooed.

Number of sex partners -- you can see that we have a progressive rise in risk as the number of sex partners increase.

History of STD, ulcerative and both non-ulcerative, any history of STD was a risk factor for HTLV I infection. Any partner from an endemic area increased the risk of HTLV I infection by a factor of three.

Sex with a prostitute also elevated the risk factor, again by a factor of about two to three. And here is where abortion comes in. Never pregnant had a risk factor of one, and ever pregnant or an abortion had a risk factor of around three and a half. What you'll see is that the risk factors are slightly different and more elevated for HTLV II.

Now, here are the risk factors for HTLV II. As you can see, we have the same magnitude of risk and decrease in risk associated with education as we did for HTLV I. Again, the same order of magnitude, a factor of about two. Here is the largest risk factor, where we had injection drug use, had a risk of 28 times for those who ever -- ever used drugs. And we only have ever injected drugs.

Transfusion is an order of factor of three, so those who have been transfused ever had three times the risk of HTLV. And here we have tattooing, and tattooing in the bivariate analysis had a highly significant elevated risk factor.

Number of sex partners in a lifetime increased, again, quite dramatically as the number of sex partners increased. From one of the first presentations, you can see that probably 50 percent of the people are in this group of more than two sex partners on the national basis. So if you want to make a sex partner cut, it's pretty difficult based on the number of exposures.

History of STD -- again, we have an elevated factor of about three, which is very similar to what you saw in the first slide for HTLV I. Any partner from an endemic area -- and these

were HTLV I endemic areas -- again, a risk elevated at about the same level. Any sex with a partner -- IDU partner, again, was about the same level of magnitude as being an injection drug user.

Okay. Sex with or as a prostitute -- again, it was a significant elevation. And here is where the abortion came in, and you can see that those who were never pregnant had a risk factor of one as the reference group, and then those who had had an abortion, at least one abortion, had a risk of almost five. We didn't have enough that we could look at gradation above one to see if there was any kind of relationship.

Now, what I did in this slide -- the next two slides, just to look at whether there was a difference in males and females in the risk factors -- these two slides -- again, on the bivariate distribution -- break them down. And you can just see that there is a significant elevation for males but not females -- again for ulcerative STD, again for males, not significant for females. This would mean that the males who have ulcerative disease are more likely to receive the virus.

Number of sex partners -- again, you can see that there is a relationship with those having more sex partners, both for males and females,

slightly higher for males, of having the HTLV I. And also, for males, a higher risk of transfusion-acquired HTLV.

For HTLV II, again, you can see that for males living overseas had an elevated risk factor. Number of sex partners was greater for females. This would support that sexual transmission is probably more important or more efficient for females than males. IDU, as a sexual partner, again, much higher for females. And transfusion is about the same.

The next part of the analysis looks at the adjusted odds ratios. And what you'll see is a lot of the risk factors disappear once you put it into the fully-loaded model. And again, the same thing that stays in is education.

We have a nice decrease with the higher educated groups. Stuck or cut with a sharp instrument stays in with a risk factor of about three. And blood transfusion now has a risk factor of about 5.6, an odds ratio of about 5.6. So it's very significant as a mode of transmission for HTLV I.

Again, still on HTLV I, the number of sex partners increased, and we have a linear increase. This is not significant. But as you get

into seven plus, there is an elevated odds ratio. Any sex partner from an endemic area, again, it stayed about the same, of the order of about two and a half.

Now we're on to HTLV II. And again, the exact same relationship you saw with I, that the more educated have less of an odds ratio of HTLV II. Stuck or cut had an elevated odds ratio of about four, so that parenteral transmission is an important factor for both the viruses.

Blood transfusion, again, is about the same order of magnitude, about four and a half. So those who have received transfusions in their lifetime are more likely to be infected with both HTLV I and HTLV II, and here you can see the injection drug use. And once you adjust for the other factors, injection drug use is about 11 times higher for those who injected drug use than those who didn't for HTLV II. Not unexpected.

Any partner of a sexual -- any sex partner of an injection drug use has the highest risk factor of about 21. So you can see that the male to female transmission is important, and that most of the females who were in the study were not drug users. But 65 percent of them had sex with male drug users. So it seems to be a very effective

mode of transmission. Number of sexual partners in a lifetime -- again, we have a nice increase.

Again, unexplained, which is probably a residual risk factor for other variables that we haven't identified, but any sex partner from an HTLV I endemic area, is also a risk factor for HTLV II. And once you adjust for all of the other factors, we still have abortion as a risk factor for HTLV II.

We're not suggesting that abortion itself is a risk factor because we have no evidence that there's a blood contamination. But it's probably a factor related to some other factor of lifestyle that's a risk factor for disease transmission.

Seventy-two percent of the HTLV-infected blood donors are females, and they are represented in our database of only 45 percent of the donors. So you can see that there is an increased risk, clearer increased risk of females of being HTLV infected.

Lifetime number of sex partners was an independent risk factor for both I and II, with increasing risk associated with increasing number of sex partners. And this supports the sexual transmission for both viruses.

Having ever received a blood transfusion, again, was a risk factor for both HTLV I and II. Elevated risk odds ratio of somewhere around four.

Low education attainment and exposure to blood through accidental needlesticks or cuts are new risk factors identified for I and II. Any association with needlesticks and cuts supports case reports of acquired HTLV infection.

History of abortion, as a significant risk factor for women, is also new. But as I said before, it's probably due to other unexplained factors that we haven't identified. IDU and sex with an IDU are the predominant risk factors in HTLV II in blood donors.

Since blood donors are prescreened for potential risk factors, you have to be careful about extrapolating this data to the general population. When you look at the small number of persons in some of these categories that we have, some of the relationships that we have might have failed to achieve statistical significance just because of the small numbers. But they might be, in future studies, worth looking at in more detail.

The other thing that we've done, as a number of you who are statisticians out there, we

have taken a .05 level as our significance, and perhaps some of the factors that we're reporting here in other studies would not be substantiated. But we have a large number of factors, and, you know, the chances of having something that's a spurious association is increased as the number of comparisons that you look at is increased.

This is a slide that I just threw in to remind myself that if, in fact, you are trying to introduce new risk factors in the screening process, we still have only five percent of the population, as Dr. Doll said, that are blood donors. However, it was interesting to me -- and I have seen the number before -- that at any time in their lives we have about 45 percent of the population had been blood donors.

So for some reason, we lose a lot of blood donors. And as you can see, this is from NHIS -- that as you go farther out, these people were -- 14 percent had donated five years previously, but the number drops quite a bit. So for some reason, people come in and at some time donate blood, but we have a very tough time in convincing them to become regular blood donors.

The next part of the presentation just looks at the type-specific HTLV I and II

seroprevalence. And as we said before, it's not very well-defined in the U.S., except in very high-risk groups. And the blood donors are a suitable population for studying both the demographic and geographical associations of I and II.

This is all persons making at least one autologous -- one non-autologous blood donation in 1991 through '95, and the REDS centers are included in this analysis. And the HTLV seropositivity was confirmed by Western Blot, and then we did typing by PCR and/or recombinant peptide EIA at the blood bank or at a standard reference lab. And then we used the same statistical procedures as we did before.

I'll just run through these, as I see a lot of people are already nodding, and just quickly -- this just gives us an idea of the rates in the blood donor population. And as you can see, we had 156 HTLV I seropositives, for a rate of nine per 100,000, versus HTLV II, a rate of 22.3 per 100,000. The overall rate is about 36 per 100,000, and we had 75 that we just couldn't type.

Here you can see by age for HTLV I, and the top line is females. And we have a clear increase with age for females and an increase age for males, and the females are always higher.

For HTLV II, we have a little different picture. We see that the prevalence peaks out at about 40 to 49, and, again, the females are much higher, by about a factor of three or so, than the males are.

Here we have our typical, in a lot of the REDS studies, east-west gradient. We have two blood centers on the west coast, and then we have our three that are central U.S. or east. And you can see that we have a clear peak in prevalence at this age group. And what we think this is is that this represents increase in drug use at about 20 years ago in this population. And the drug use patterns were a lot greater on the west coast than the east coast.

These are looking at the modeling of HTLV I. And again, you'll see quite similar patterns -- that the older people have a higher risk, and it doesn't vary a great deal. That risk for females is twice as high for females as males, and that the black versus white is about ten-fold. The other groups are about two- to three-fold. It isn't significant for the Asians, but it is a significant factor for Hispanics.

Birthplace outside the U.S. is a risk factor, and as is first-time donors. First-time

donors had a prevalence rate about 2.8 times as high as repeat donors. We had another group that we had first-time and repeat. These are people who came back and only donated once. These are people who came back and were first-time donors but then became repeat donors. And those people had a very low incidence. It's strange, and I think because they are most -- they've been recently screened, and, therefore, their rates are lower.

Again, this is interesting, that the HCV -- those who were serologically positive had a five-fold higher odds ratio of being HTLV I infected.

Same type of distributions you'll see, but here you see for HTLV II, you see the big increase in the central age group of 40 to 49. Females were about three times as high as males.

Again, here we have this east-west effect. So what you can do is look at, on the west, and you can see that the blacks were significantly higher than whites. The reference group is eastern whites, which are the lowest. But, again, you can see that eastern blacks and eastern Hispanics, and then eastern Asians, are higher risks than are the eastern whites. So there are some racial distributions.

Again, the same as we saw in the case control study. The odds ratio for high school or less is higher, so it decreases with increasing education, which is a proxy SES variable. You're safer if you're born outside the United States for HTLV II. Probably more likely you're not a drug user.

Donor status -- again, first-time donors had a much higher odds ratio than did repeat donors. And the HTLV serology -- 25 times higher if you're HCV positive to be HTLV infected, than you are if you're HCV negative. Again, this would indicate that it's probably a common route of transmission.

I'll skip through the conclusions because we've already gone through these. And I'll skip these slides. These are just a more detailed breakdown of the demographics.

(Applause.)

DR. DAYTON: So we have quite a lot of time now for a question period, and then we'll have a brief break for coffee or something.

DR. ALAN WILLIAMS: Alan Williams, Red Cross Holland Labs.

George, you mentioned in the case control study that you have a lot of simultaneous

variables going on there. If you apply a 99 percent confidence interval, do you lose many of those?

DR. SCHREIBER: Yes, we would, and I can't tell you which ones. But, you know, most of those that are hovering around an odds ratio of about two would disappear, and you're left with the ones that are, you know, order of odds ratios of five or so. And the ones that certainly stay in are the relationships with the injection drug use.

DR. RUTA: Martin Ruta. Actually, I wanted to ask the last three speakers -- I was having trouble synthesizing the data from the three talks. I was wondering if we could ask all three, if we went through just point by point and looked at what we found for IV drug users, in terms of HIV, HCV, HTLV, and then did the same thing with sex workers, and the same thing with MSMs. And then, if there's any data on partners, just so I can see if I can try and compile everything into one place.

So if I could ask the other two speakers -- previous speakers to go up, and maybe we'll try it point by point. This will help me out in trying to put all of the data together, if you don't mind.

DR. SCHREIBER: Clearly, for HTLV II, as I said, that intravenous drug use is the highest

risk factor. And sex with an IV drug user is also a very significant risk factor.

DR. GLYNN: Yeah. We also found that injection drug use was the highest risk factor and the most prevalent among the cases. The odds ratio there was about 15, the final model. And sex with an injection drug user was also increased -- odds ratio of about six. And the highest one for HCV that we found was transfusion, but that was true only among non-injection drug user. That was an odds ratio of about 11.

DR. RUTA: George, did you find something similar for transfusion?

DR. SCHREIBER: For transfusion, there was a risk factor of about four, an odds ratio of about four, for both HTLV I and II. It's just transfusion ever, so we don't know -- we don't, you know, know the time period. But probably most of them would be unscreened blood.

DR. GLYNN: The same thing for the HCV case controls. The blood transfusion we had, actually, a question asking if it was before May 19 of '90 or after. But, unfortunately, we have so few people saying after May of 1990 that we can't tell the difference.

DR. RUTA: Was there any information on sex workers or MSMs for HTLV or HCV? Were those asked? Was there --

DR. GLYNN: For sex workers?

DR. RUTA: Yeah.

DR. GLYNN: Yeah. The one I saw for HCV showed that we did not have a significant association after. It just went for injection drug use. Before adjustment there was one, but not after adjustment.

DR. SCHREIBER: And we had the same, that after you adjusted for the other factors, there was no relationship with being a prostitute and either HTLV I or HTLV II. And there was no relationship with male to male sex in our analysis. They dropped out, even in the bivariate.

DR. RUTA: Ken?

DR. CLARK: For my data on the HIV risk categories and the prevalence, it was separated by both men -- or by men and women, so it's hard for me to give you a combined estimate. But for me, certainly the highest risk category was male sex with another male. And the lowest categories were injecting drug use and heterosexual contact, and the no reported risk group fell between those.

For women, the lowest was injecting drug use, and the no reported risk group in the heterosexual contact made up the vast majority of those, with heterosexual contact being slightly less frequent than -- or less prevalent than the no reported risk group.

DR. RUTA: Okay. Then maybe a little bit more difficult question. Is this related to truth telling within these, you know, populations here? Certainly, we see high rates of HTLV and HCV in IV drug users. One might expect that, you know, that correlates well. With HIV, I guess we see high rates in MSMs and in IV drug users also, is that right? But we don't see -- there seems to be a disparity there in terms of the truth telling. Is that fair?

DR. CLARK: Well, for HIV, we didn't look at the data that way for this study. We looked at it among all donors, breaking them into the risk groups. But we didn't look at rates in each individual risk group per se; the reverse of that.

DR. RUTA: Okay. Thank you.

DR. DAYTON: Do we have any further questions or comments on these talks?

All right. Why don't we take a coffee break. And I think the schedule calls for us to be back here at 2:45.

(Whereupon, the proceedings in the foregoing matter went off the record at 2:28 p.m. and went back on the record at 2:46 p.m.)

DR. DAYTON: Perhaps we can begin to get together for the next session.

The next speaker will be Alan Williams, who is going to talk on unreported risk behaviors.

DR. ALAN WILLIAMS: Okay. We're going to make a dramatic shift in focus here from risk behaviors in donors with infection to the risk behaviors in donors without infection.

When the REDS study got started in the late 1980s, there were a number of different aspects of the study that were going to be pursued. But one in particular was the fact that a number of us had been involved in interview studies of donors who had been found positive for one infectious disease marker or another.

And as a result of those interview studies, we found that most of those former donors, when interviewed, had a risk factor that should have

prevented their donation in the first place. And this was true for HIV and for hepatitis as well.

So what we tried to come up with was some mechanism to measure this factor in donors who are active but not coming up positive in infectious disease screening tests. And, in fact, in running some of the case control studies, if you did a face-to-face interview with controls, you would get risk factors appearing as well.

So based on some early information coming out of some other national studies -- for instance, Dr. Catania at UCSF had just completed a general population survey of AIDS risk factors, and Nork had done some. We tried to put together a process whereby we could use a survey methodology, send surveys to active donors, and try to see if we could get answers to the same risk questions that they had been asked at the time of donation, and measure that differential between those who had told the truth at the time of donation and those who hadn't.

So the mechanism we ended up with after some piloting was first applied to a survey in 1993, and what we did was use anonymous monthly mail surveys sent to the active blood donor population within about six weeks of their donation event.

Because REDS has a very extensive database, we selected a highly controlled, weighted random sample of the database for each site, and then the survey mechanisms that we used consisted of an advance letter describing the survey and the fact that the donor would be receiving the survey instrument in a couple of weeks, followed by the survey instrument itself.

And in the first survey we actually used followup measures that involved sending out a complete separate survey of a different color with an explanatory letter that because this was anonymous we wouldn't know who had replied.

And in the 1993 survey, conducted between April and December of 1993, we sampled 50,000 subjects in the sampling frame and had a 69 percent response rate, comprising 34,700 donors.

Results from that survey have largely been published. I think the major publication came out in JAMA last year, in which we described what we called deferrable risk factors in donors, and we found that in looking at risk factors which should have resulted in deferral of an individual, which we call deferrable risk, using the survey mechanism we found that 1.9 percent of donors following the

survey procedure would admit to one of these deferrable risk factors.

And then, subsequent to that, we were able to make some associations with other variables. For instance, we also measured a three-month risk and found 0.4 percent of deferrable risk at three months. And each of these risk factors was found with a higher prevalence in males in first-time donors and donors who used the confidential exclusion process and donors who admitted on a different question that they, in fact, had donated blood for purposes of receiving an HIV test result.

Of interest, I think, in the first-time versus repeat donor stratification, we actually found the ratio of risk -- first-time donors had a 1.6-fold higher relative prevalence of risk than the repeat donors. And I think this correlates quite nicely with the lower sensitivity HIV test information, reflecting incidence that Mike Busch presented a little earlier. Because, in fact, this is a population that infected individuals are most likely to arise from.

A second publication described some considerations surrounding HIV test seeking. In the '93 survey, we found six percent of donors admitted to donating blood at some time in their life for

purposes of receiving an HIV test, and 3.2 percent of those donors acknowledged that activity within the previous year. And this publication uses those figures and compares them with likely window period reductions associated with p24 antigen reduction and tests some theoretical models on that basis.

And then, a third paper uses some -- the other factors from the survey to identify a group of donors who do not have markers, did not use CUE, and some other factors related to what we termed a "safe blood donor" and some of the factors that would enhance their return as blood donors in the future.

Now, following the 1993 survey data collection, we ran a pilot survey in 1995, and this was primarily done to pilot some information related to donation incentives, because although this was a popular concern there was really very little data in the field related to incentives or to test-seeking activities.

Based on the results from that pilot test, we put together another survey to be conducted in this year, 1998, and I want to emphasize very strongly that we didn't want to present five-year old data for this conference. We wanted to present the latest data. but what I'm going to show you today reflects two waves of survey data, and the

total sampling frame is going to be 104,000 donors. And the data shown today represents about 14,300 donors. So it is very preliminary.

It hasn't been corrected for the oversampling that was used in this survey. And, in fact, we have three additional sites in the survey, other than the five REDS sites that we had earlier.

So for this 1998 survey, which is in the field now, we're targeting 104,000 donors at eight sites, including New York Blood Center and two smaller sites. It will run from April through October of 1998, and we primarily want to do this additional survey to further study the deferrable risk findings of the earlier study, look a little deeper into the relationship with other donation variables, look specifically at the reasons that donors do not reveal risk at the time of donation, look hard at donation incentives.

And, in fact, a sample size was built around an attempt to get statistically valid information to look at time off from work as a donation incentive and its relation to risk. And then, finally, we wanted to get more information about HIV test seeking.

Now, shown here is a comparison between some of the individual risk values between the 1993

and the 1998 surveys. And these values for the 1993 survey are published in the JAMA paper.

For injection drug use ever, which, of course, is a deferral criteria, in 1993 we had a half percent reporting that risk. To date, in 1998, we have 0.2 percent. Now, there may or may not be a true different there. I think we'll have to get further in the survey and correct for the different centers and such to see if that's real. Nonetheless, there is some evidence that we might have a little lower data for that particular risk.

We added a new question based on Dr. McCurdy's suggestion that in addition to injecting drug use we add a question about the injection of steroids as a risk factor. We didn't ask this in 1993, but we have a .1 percent return rate on that question.

Sexual contact with an IDU in the past 12 months -- got pretty close data, .4 percent versus .3 percent so far. Males who have had contact with another male since 1977 -- obviously, a deferral question -- .6 percent in '93, and so far it's running one percent in 1998.

Again, with the addition of the other sites, it will remain to be seen whether this is a true change or not. But at this magnitude, it may

well be significant, once the study is complete if this trend holds.

Sex with a commercial sex worker -- also on this survey -- a half percent in 1993 and 0.3 percent in 1998, to date.

Now, we did ask some other questions related to the finding of risk factors in donors. And one of the questions we ask is whether the donor felt they had sufficient privacy at the time of screening, because, as you might imagine, if a donor is there with colleagues or a spouse, or co-workers, that a perception of insufficient privacy when going through this very sensitive interview screening process could, in fact, compromise a correct answer. And we wanted to see if we were getting any variance between risk factors and overall donors in relation to privacy.

So for all donors -- and this is 1998 data -- four percent claimed that they had insufficient privacy at the time of screening.

For the IDU ever question, that went up a little bit, 7.7 percent. Sex with an IDU, 6.3 percent. For the males, sex with male risk factor, considerably higher, 16.5 percent. And this parallels a similar finding for 1993, that this was a common claim among males who had had sex with

males, that their privacy was compromised at the time of donation.

And for those individuals who had sex with a commercial sex worker, virtually all males, the factor was 12.8 percent; again, compared to four percent overall.

Another thing, as I mentioned, we wanted to look at was donation specifically to receive an HIV test. The background numbers for this factor are somewhat lower than they were in 1993, and I suspect this might be a true finding, given the size of the group and the overall prevalence. The fact in 1998 for donors claiming this ever was two percent versus 6.1 percent in 1993, and donating for such a reason in the past year is one percent in '98 versus 3.1 percent in the earlier survey.

But you can see there is quite a bit of variance in relation to donors who also claimed a risk factor. Interestingly, in comparison to some of the recent versus remote risk for IV drug users, you see that almost 21 percent of those donors with an IV drug user risk had ever donated for the purpose of HIV test result. But in the past year, it was 2.6 percent, considerably lower.

And this can be contrasted with some of the other risk groups -- for instance, the steroid

injectors where the ever risk is 18.8 percent, but about half that in the past year. Individuals who had had sex with an IV injecting drug user in the past 12 months, not much difference between the two. In fact, most of this reflects recent concern about HIV test status, probably reflecting recent risk. And MSM risk -- 13.9 percent ever versus 6-1/2 percent in the past year.

Also, one of the highest levels from males who have had contact with a commercial sex worker. Twenty-one percent, about a fifth of these individuals, donated ever primarily to receive an HIV test, and 10 percent in the past year. So I think in the whole area of why do people donate blood, there is a wide variety of reasons. But I think specifically within some of the risk groups that we're concerned about, donation to receive an HIV test result is a substantial motivator.

We also had a question related to prior testing for HIV elsewhere, prior to this donation, other than at a blood center. You can see that the factor for overall donors may or may not be high, depending on whether a person had been hospitalized or tested as part of a routine medical workup.

But overall, 25 percent of donors claimed they had been tested for HIV elsewhere, and

this is higher in virtually all of the other risk categories -- 50 percent in injecting drug users, injecting steroids; 56 percent in those who knew they had had sex with an IV drug user; 50 percent in males who had sex with other males; and a little bit higher in those women who -- largely women who had answered the question that, yes, that they had received money or drugs for sex since 1997.

I didn't have it on the slide, but the prevalence of this factor in this 1998 survey is 0.7 percent.

So some preliminary data conclusions from the 1998 survey -- I think necessarily the conclusions are sort of soft because this is in an early phase. We haven't done some of the statistics. But I think it's notable to say deferrable risks are still measurable in the active donor population. The proportion of donors with MSM risk since 1977 may be increasing, and I think as the survey matures we'll be able to say that with a little more power.

Donation to receive results of HIV testing may be declining in the general donor population, but it does remain high in at-risk donors, and appears to be a motivator for donation.

There are a couple of other questions, which I didn't put on the slides, but I think in light of some of today's discussions and the test-seeking variable, that it would be useful to point out.

We had a couple of true-false questions in the back of the survey, and what I'll do is just read the question. All of these are true-false questions. And I think some of the answers might be sort of telling and provide some lead as to where some of the education of donors might be done in the near future to help improve the situation.

First statement -- true or false -- it's okay to donate blood in order to be tested for the AIDS virus. 22.4 percent of donors said true. 13.2 percent said they didn't know. Probably equivalent to a true answer in that they didn't know to, you know, have that defer potential blood donation.

Second question -- it's probably okay for someone to donate blood, even if he or she has engaged in AIDS risk behaviors, because all blood is tested and thrown away if it is infected. Got a true for that statement from 9.8 percent of donors, and don't know from 13.6 percent.

And for those of you involved in some of the HIV seropositivity interview studies, you know a

common response in donors who receive such an interview is, "Well, I thought all of the blood would be tested, and, you know, it would protect the recipient because of the high sensitivity of the test."

So clearly, some proportion of donors don't understand the concept of window period.

And then, finally, a specific window period question. Is it possible that a person infected with the AIDS virus in the past two weeks will not be detected by routine blood testing done by the blood bank? 16.1 percent said no, and only 0.2 percent said not sure.

So I think this is -- you know, I've often had questions, "Okay. These are the data. What do we do about it?" I think if we start looking at the motivations of donors who come in inappropriately and don't defer for risk, as well as answers to some of the questions like this as to where educational incentives might be targeted, we can hopefully get a little broader perspective on some of the issues.

The 1998 donor survey, the last data collection will be on October donations, which, of course, have already been made. It takes about four to five months to complete the process after a given

wave of donations. So I expect in the next six to eight months this should be completed and ready for formal analysis.

Thank you.

(Applause.)

DR. DAYTON: Thank you, Alan.

The next talk will be from Celso Bianco on self-identification of deferral risk.

DR. BIANCO: I'll speak from here because it's easier to manage this.

What I attempted to do was to collect some of the data that we have at New York Blood Center regarding the questions that we are dealing with. Obviously, not all of them. Many of the questions have no answer.

But the first question, obviously, was that -- I thought that somebody else was going to touch today -- but if we ask: what happened to confidential unit exclusion in recent years? And I can tell you that at least in New York, and we were very effective in doing that in the early days.

We have seen a steady decline of the HIV positive donors that you confidential self-exclusion. Actually, it's a surprise sometimes these days. In the last two years, we had none, and last year, in 1997, we had one.

The other thing that I find interesting in this slide -- as I saw the data presented by Ken Clark, I was very concerned about an increase in the number of HIV positives -- a very nice trend until 1996. But I see his slide combining the 15 centers, that this was true probably for the other centers, too, unless all of the increase comes from us.

This is the same exact type of data, but just taking the number of donors that were HIV positive every year and the number of ones that shows the confidential self-exclude.

Now, the next -- so the very short points that we can make regarding that is that a very small proportion of donors uses confidential unit exclusion. And very few, if any, of these donors who currently use confidential self-exclusion are positive for HIV.

Now, I'd like to -- we collect data about all of the deferrals regarding medical questions. And we tried to put together -- I tried to put together in a table some of these major figures to give us a perspective about all of the deferrals.

And I tried to divide them more or less in four types. Self-exclusion we talked about. But deferrals, because of non-interpretive questions,

were because hemoglobin, blood pressure, temperature, interpretive questions like questions, did you ever receive -- were exposed to hepatitis or received a transfusion? Or did you travel somewhere?

And then deferrals associated with risk behavior directly related to questions, direct questions about risk behavior.

Twenty-three percent of all donors between May '97 and April '98 were deferred. That was 100,000 donors out of a total of 454,000 donors. As they came to the donation site, they completed their registration form and they did not donate.

Many of these deferrals, the most frequent cause for deferral was the level of hemoglobin did not reach the 12.5 percent. And those were 5.7 percent of all donors. The next was among the non-interpretive -- blood pressure, .9 percent, temperature, which I think is a valid point for us to think about when we think about emerging infections.

General questions -- travel, cancer, medications, all lumped together -- represent 14 percent. Infectious disease -- about 1.4 percent. And actual risk -- if you ask questions about risk behavior -- they are the focus of our discussion

today -- represent only .2 percent of all donors, 914. How do they break? How do they distribute?

Donors refer risk behavior under the right conditions. We don't know the sensitivity of the process, but they do refer, when asked directly, if they had taken drugs, or if they had sex with somebody that took drugs. They tell you -- and we had 121 donors that had sex with males since 1977, sex with an HIV positive individual, given or taken money for sex.

Sexually transmitted disease questions were very important in terms of detecting these behaviors, and we had 62 donors that had needle tracks and were deferred because of identifiable needle tracks.

Also, if many of you don't recall, but the older ones will, in 1990 we started asking direct questions of our donors. Until prior to 1990, we only -- most of the centers would ask the questions, either in writing or ask very generic questions about risk behavior. And at that time, actually, we did a study in which we analyzed six months of donations, from April '99 to March -- a year of donations. And what we saw was a substantial increase in the risk of individuals that

revealed -- and the number of individuals that revealed risk behavior.

Similarly, more recently, there was a lot of discussion about snorting cocaine. We do not know the impact of those. I could say that the impact of the prior one may be in the graph that Dr. Clark showed -- the substantial decrease on the number of HIV positive donations between '90 and '92. That maybe that was one of the contributors.

Here we had a 12-fold increase in the number of individuals that were deferred when we added the question about snorting cocaine. We do not know, obviously, with these numbers what the impact of this is in the number of HCV positives or in the safety.

So if we ask the question: do donors review risk behavior during medical history? yes, they review risk behavior. Those donors, unfortunately -- or fortunately, for the blood supply. But, unfortunately, for the answer to the questions that we have today, they are deferred up front. Specimens are not collected, and there is no testing.

Consequently, we do not know the sensitivity, the specificity, the positive predictive value, and the negative predictive value,

of the questions that we ask. Actually, my fantasy is before I retire is to be part of a study where we would collect samples from all of the deferred donors -- Dr. Nemo -- and be able to truly measure the value of the questions into several shapes and forms that we ask.

We also know that donors who respond affirmatively to risk behavior questions or use CUE do not present additional risk to the blood supply because they are deferred permanently or temporarily. We may change to '77, we may change everything. They are truthful, and they will continue to do the -- to provide the correct answers.

All of the disease transmissions actually associated with the window period of seroconversion are associated with those donors who deny risk in medical history and do not utilize CUE for their -- to defer themselves.

So in terms of corollaries -- and I'm putting these here just to challenge ourselves to discuss a little bit more these issues that we tried to discuss this morning -- is that my point of view is that changes in medical history questions in deferral periods do not affect individuals who deny risk behavior, and they are going to continue in

permanent denial. For them, we have to rely on what is provided to us by the other means -- testing. There will be NAT testing and all other methods that we use.

These questions only affect individuals who are truthful in their answers, and changes in deferral periods are unlikely to change their answers. My concern is that since we rely a lot on medical history questions, because we have this perception that, according to the data from Dr. Williams that we just heard, that they are 98.1 percent sensitive or specific. We continue to add complexity to medical history. If we take the standard AABB medical history, I believe it is now 37, 38 questions.

So in that complexity, I think that we divert the attention of the donor from the important subjects that the donor has to deal with. After a few questions, as we discuss with them and we talk with them, they are lost. They are thinking about something else. They are thinking about the football game or something else and just automatically checking questions. And only when we challenge them again with critical questions about risk behavior sometimes some of them will come back.

But the complexity of the questions -- and we know that. We know that for many years, since the famous American Institute of Research Donna Mayo Study, that the complexity of the questions interfere with the accuracy of their answers. And I'd like us to continue to try to focus on that.

We are also trying to deal with the issue of perception of discrimination and clear criteria. Really, the question that we -- about male sex with males since '77, focus attention to events that occurred more than 20 years ago instead of events that occurred within the current window period for HIV -- 16 to 22 days.

So, and some of my points that I'd like to raise is that the major known risk of transmission of infection by transfusion is associated with windows. Many donors review risk behavior during history, so history contributes to the process.

And when we compare the prevalence of markers in the general population, like we heard today, of four percent for HCV -- or three percent for HCV in certain populations, and the prevalence among blood donors that is .2 percent, we know that

we improved that selection by 20-fold. But we do not measure those.

Additional questions in history increase the number of deferrals, but we don't know if this is specific or not. Some donors are positive for infectious disease and do not reveal risk. They do not associate risk with their behavior.

So the major risk of transmission of infection is associated with individuals that do not reveal risk. There is no reason to assume that changes in deferral periods induce individuals to be truthful, and we need data about sensitivity and specificity of medical history. And I also would like to say that the differences in deferral periods for sex between men and sex with a prostitute are not based in data.

Thank you.

(Applause.)

DR. DAYTON: We're now going to have a brief talk from Dr. Zuck on interactive questionnaire.

DR. ZUCK: Well, I want to thank the organizers of the conference. When the announcement came out it said, "If you want to present anything, send this little form back." Well, we did. And that's why we're here, because we thought it

pertained a little bit to where we might be going and it solved some of the problems.

I apologize for my hoarseness. I'm taking a drug, which I think may be worse than the condition for which I am taking the drug.

(Laughter.)

We've been interested -- prior when I was at the FDA, I was interested, and, in fact, the FDA funded the AIR study, which isn't widely known but that is, in fact, the case. And I've been interested ever since personally in it but not been able to really get much interest in it. But I want to present a little bit today of the system that we had designed and developed -- designed and has been funded by the SBI as an SBIR.

The system purposes -- increase donor history accuracy and consistency. And we know from the AIR study, and we know from the REDS data, that we can improve perhaps things in this area.

We rely on perhaps a behavioral memory jog, improved privacy, and eliminate missing elements. Those are questions unanswered but which the nursing staff did not recognize are unanswered, and I would urge that none of you look at this issue in your own center because you end up with a lot of

recalls because that's what happened to us when we looked at it.

I'm not saying recalls are unjustified. I'm just saying you'll have a lot of missing elements -- that is, unanswered questions -- which affect the safety of the donations.

The increase in process efficiency, we believe, essentially will make the program costs neutral. We certainly have yet to prove that.

The Phase I SBIR grant from Heart/Lung is the Talisman for -- to Paul and to me. To determine system feasibility is Phase I, compare efficacy to conventional screening, both related to missing elements, donor staff acceptability, and compare repeat donor responses. We did that when we did the AIR study and found 35 inconsistent responses in 9,000 donors. So this is not a minor issue of people who will change.

The critique of the SBIR said we were not going to prove we made donors safety -- the donors supply safety, and that's true. With the current infection rates, it requires over 30,000 donations to even come close. I mean, 10 times that number to come close to finding reduction in HIV. It's just not possible.

But we do think we can improve the efficiency. This is a cartoon of a rejected donor, a donor going through the process, and ending up in an interactive video environment, where they are alone in a booth. And they have taken to the booth the preprinted donor form, which is printed by the laser printer as they are now, but all of the questions that are asked during the interactive video screening are blank.

They take that form to a booth in which they can initiate -- it says, "If you start the screening, push here." And it's interactive in terms of the donor being all alone, being asked the questions that are much like the questions we ask now, but a couple little modifications.

Each screen is accompanied by a voice. This is Dr. Carey, who did a very good job making the voice very clear. And beside it is a picture. Now, this is a picture related to homosexuality. We tried to make the pictures as neutral as we could. We'll show you a couple.

This is the one for inoculation or vaccination. This is one for a transfusion. This is a screen -- yes, no. Next.

If they have a question mark, the system moves on, and Dr. Carey quits asking the question.

Every question is read. This part inside the blue box is read by Dr. Carey. And it doesn't do you any good to answer the question. You can't just blop, blop, blop, blop through it. You have to wait until she is done.

And lastly, this, "Have you been on a wonderful vacation recently?"

(Laughter.)

One of the objectives, too, is to make the interview more real for the donor, something that they can really relate to.

Now, if they push "no" for a question, or "we don't know" for a question, and if the answer is exclusionary, they really don't know. When they complete the screening, there is a button on the side of the computer. Push "end," okay? Very creative. Push "end."

And the nurses' station is a series of lights that go off and to tell them which booth, in fact, has a donor completed. And then they will push the -- and this is the "end" screen. And they will go back and rescreen those questions that either were not understood or were skipped to go on to an additional question until all of the questions have been answered or completed to the satisfaction of the screening nurse.

The form that you saw that was partially blank, obviously, you can't read, but that form is then run through a laser printer. Based on the answers that were given, and the nurse having screened that all of the answers were, in fact, given.

One of the issues which to go back to just a second -- if at any time during the interview one of the donors believes that somebody has opened the door and walked in the room and it's not private, they push the screen and the question being asked goes blank and will not reappear until they push it again when the privacy threat has disappeared.

This is, again, what appears -- prints from the combination of the blank material which was given before, and this now fills in the history to complete the donation.

There's a long history of this, actually. In the winter of 1997, the safety system got the go-ahead to be sold by Talisman. In the fall of 1998, Hoxworth filed a CBE-30 change. We were told that the reason we did that is there is no logic in this system. It does not define a donor who is or is not acceptable. It presents to the nurse the material to make the nurse make the

decision. So we were trying to avoid having a 510(k), but by the same time improve the accuracy of the screen.

So we took the donor logic out, and the nurse makes the determination, as they do now. We feel that this change -- we filed the FDA -- CBE-30. They wrote us a letter saying, "No, no, no. We don't think so. We think you have to have a PAS." So, right now, it's being treated as a PAS, and it's under review. That letter was on the 29th of September.

We're hopeful of getting it up. The system is installed. Electronics are all installed. So we are -- and the forms have all been bought. We're ready to go. And we think that the exit questionnaires and the -- we were going to look at the data that has been generated by this system. It will helpfully refine and improve our accuracy of donor screening.

Thank you very much, and thank you for giving me the time.

(Applause.)

DR. DAYTON: Do we have any questions for any of the last three speakers? If not, why don't we just go right ahead and have Sue Stramer give her talk on -- well, it's a long talk --

sensitivity and specificity of donor screening tests for HIV, HBV, HCV, HTLV.

Can you do all of that?

DR. STRAMER: I'll try. Thank you. I hope I can cover the lengthy topic that was given to me.

So in trying to think about how to address this, it's really a potpourri of a number of my thoughts. So you'll bear with me. And if I miss something, we can review anything that's not there.

Okay. Today what we've been covering is donor populations and donor screening questions. The topic that I'm now transitioning to is donor testing. Mike Busch covered donor testing this morning in incidence and prevalence rates, but I'm going to cover the specifics of donor testing as they relate to the performance characteristics of the test and sensitivity and specificity.

Firstly, we have to decide what truth is. Truth is either present in the population as a disease or absent. And then what your test is required to do is either detect the presence of the disease or not detect individuals as reactive who are not present -- who do not have the disease.

But as we all know, and we are here today to talk about, the false negatives do occur,

albeit infrequently, and false positives do also occur.

Just to run through some basic definitions so you understand how the talk is structured -- sensitivity is defined as the proportion of positive results obtained when testing a population known to have the disease. This is basically defined as truth, and it's independent of prevalence. So here are the false negative rates, in addition to what we detect have an important impact.

Conversely, when we're talking about specificity, it's the proportion of negative results obtained when testing a population known to be free of the disease -- again, independent of prevalence. So it's the true negatives divided by the combination of the true negatives, the sum of true negatives plus any false positives. And we're all painfully aware of specificity, in some cases, on screening tests.

Other parameters that are used to assess test performance really have a dependency on the prevalence, and they really say how well is the test doing in that specific population. And their positive predictive value -- that is, the proportion of results that are true positive, which now also

includes the false positive results. It's really, how good is this test performing in the total positive population? And negative predictor value, which is the proportion of results that are true negatives. So in this case, the denominator includes true negatives and false negatives.

The tests we use today -- I do want to emphasize people say that the blood supply is safer than it has ever been, attributable in large part to the quality of the screening tests, which is absolutely true. And they go through the rigors of intensive clinical trials, FDA reviews, questions, and usually sets of trials to address any FDA questions.

And just in a nutshell, for those of you who have never been through clinical trial, I just wanted to comment on what some of the rigors are that the tests do go through. Number one is reproducibility. And, again, this is really only a thumbnail sketch.

Obviously, the manufacturing reproducibility of a test must be demonstrated, and that all technicians and independent sites outside of where the test is manufactured can reliably run the assay. Other parameters are specificity, and

generally large numbers of routine blood or plasma donors are run.

In running a trial, you need to have confirmatory strategy, should be required, and in some of the recent screening assays that we use today, as Mike also highlighted this morning, confirmatory strategy are poor or lacking.

Also under consideration during the specificity portions are the donor management issues. What do we do with reactive donors? Other challenges that the test must go through are interfering substances, such as other disease states, known assay inhibitors, or other disease agents.

But where I'm going to focus most of my time is on sensitivity of the test. And sensitivity is assessed in multiple ways through clinical trials. The most common way we do them now, really, to get at the root of the window period reduction issue is to look at seroconversion panel testing. And there are many commercially available panels, and this is readily done for agents such as HIV, HBV, and HCV, not so much for HTLV. And there are other complications with HTLV qualifications.

Routinely, you have to run your pedigreed samples from your disease state

population, such as AIDS patients or people with known hepatitis. Also, another way to address sensitivity and weak sensitivity is to run dilutional panels. This has always been historically done and probably offers the least amount of valuable data, since this doesn't really tell you the breadth of sensitivity.

It just tells you the end point of one particular sample. It's useful if you want to compare tests or compare lots over time. But basically, it doesn't tell you anything about the inherent performance of the test.

One very useful tool is to take your test -- firstly, knowing what is truth, if we believe a confirmatory test is truth, to run that as your screen and to define positivity, and then run your test under consideration against that population.

Leaving that aside, let me go to some specifics. This is the one slide that I will show of Red Cross data, and it just shows you what we have today as far as number of confirmed positive donations per 100,000 total. And the numbers in parentheses indicate the number -- the percent of confirmed positives of the total. So we have six HIV positives per 100,000. That's eight percent.

But here I have put in this other column just to let you see what the negatives -- or how many donors we lose during this process. So for the six positives we get, we lose in deferrals 76 false positives. For HBsAg, the positive predictive value, if you will, of the test is much higher when you do the confirmatory procedure. And we really -- the number of losses is only a third of what we detect as true positives.

HCV is another test that has performed well -- that is, the screening test. Very stable over time with a relatively reliable confirmatory test, at least for the 2.0 generation.

Anti-HTLV, as Mike pointed out, is highly problematic because the test, over different test manufacturers, has not been consistent as far as specificity, and because of false positives. And confirmatory, it has also yielded many, many false positive deferral notices to donors. It's difficult to assess what the sensitivity over time of the HTLV test is, and true positives, because it has been cluttered by so many false positive results that we have been getting.

Core I just put down here to round out the balance. This is a relative proportion. We don't know how many are truly confirmed positive for

anti-HBC, and this is based on an algorithm that's from Gary Tegmeier at the Community Blood Center of Greater Kansas City, where his confirmatory algorithm includes running a second licensed anti-core test in that anti-HBS.

So if you look at those kinds of data and apply them to our numbers, this is basically what you would see -- another two-thirds of donors lost because of false positive test results.

One way that I'm going to show current test performance, and really let you see what is in development that is a comparison of what we have now to what's in the future -- because to address questions about changing deferral categories or questions, I think one important thing to note is, what is in the future and how will testing improve?

So I've taken some of the slides, some of the information presented at the recent Blood Products Advisory Committee meeting on the PRISM clinical trials, to be able to show you a benchmark of where we are, again, and where we're going.

If you look at the four markers that were tested in this clinical trial, and look at the number of repeat reactives relative to the supplemental test positive, this is the truth line here. You see for two of the markers -- HTLV I and

HCV -- basically no difference for pedigreed samples.

In core, there was a discrepancy between test of record and the PRISM, and I guess I should have said in the beginning the PRISM is a single operational unit that does everything. It's a totally automated system. It runs all of the assays, qualifies all of the reagents, so that the operator has to do nothing besides add the samples and press the go button.

So in addition to assay performance, I will talk about errors related to -- decreased errors with the use of increased automation.

But the one thing that I do want to talk about, and one way that we can enhance our current level of test sensitivity right now, is in the area of HBsAg. We'll talk about improvements we can make in sensitivity of HIV and HCV with the implementation of genome amplification testing.

But really, the horizon for immediate tests for HBV DNA are not available. And there really is a great opportunity for us to detect more infected hepatitis B individuals based on improved serology. And this system really represents one way to get there.

Okay. In the clinical study, 25 HBsAg seroconverters were tested, and these data were presented at AABB. But one thing that is really interesting -- if you look at the HBsAg positive period, which in most of our cartoons of the HBsAg serologic periods have shown an HBsAg positive period of about 56 days. Interestingly enough, what PRISM has done with improved detection of HBsAg has narrowed the front end of that window or extended HBsAg into the window by 6.8 days.

Interestingly enough, if you look at the other end of the HBsAg window where anti-core is present, it has also added another 12.6 days. So it has really added considerable length of HBsAg detection to what we believe we have currently. And if you count -- use these two periods of time with the incidence, you can calculate how many additional HBsAg donors would have been detected had we been using -- if we are using the system. And this is, again, data generated in the clinical trials.

Looking at their clinical trials in total, relative to test of record, looking at all categories of samples, there were an additional 28 HBsAg confirmed positive samples detected using the system. And this really relates to better analytical sensitivity for both HBsAg, subtypes ad

and ay. So there are -- even without talking about test errors or variant detection, which I will, there is considerable improvement that can be made even with serology.

With HTLV I, the situation is very difficult because panels are difficult or impossible to come by. So frequently, what's used are dilution series, and, really, I don't believe they have a lot of meaning. Although interestingly enough, you do see a lot more dilutional strength with this test under consideration, as compared to the EIAs.

This slide shows you now what HTLV -- if you're relying on dilutional sensitivity, or even signal strength of an assay, one of the points I want to make on this slide is how misleading that can be. But the main point of this slide, if you look at the turquoise line here, is at the Red Cross we have been through three major changes in HTLV screening assays. And this blue line could be considered our relative repeat reactive rate for the number of samples per week that come into my laboratory for confirmatory testing.

And if you look at the Abbott -- and I didn't show you the line since 1990 -- it was pretty consistent at a number that really ends here. We

converted it to another test, and our repeat reactive rate shot up. So specificity of this test was considerably poorer.

We converted to the HTLV I/II assay as soon as it was licensed, and for the first couple of months or weeks the test performed very, very well. And then, as I understand it, there was a change required to one of the CBER lot release panel members to increase the signal from a very weak reactive S to CO of one to two to greater than two. So this required the manufacturer within their PLA license to modify their kit components to try to increase an artificial sample to have a higher S to CO value.

And what that really resulted in was a tremendous loss in specificity without knowing what that increase in sensitivity would really buy us in additional detected samples, which I'm guessing would be few, if none -- none or few.

Anyway, in talking about HTLV specificity -- Mike referred to this earlier in his slide -- but how this translates to confirmed positives is as follows. Historically, since the beginning of HTLV screening in the blood donor population, we have been seeing a confirmed positive rate of about 10 per 100,000.

As we converted to this other screening test, not only were the repeat reactive rates higher, but because we had the misfortune of using the only blot available, which used the same antigens as the screening test, what we wind up doing is artificially confirming the repeat reactives.

So what we had here was our prevalence then went from 10 per 100,000 to 23 per 100,000, just as an artifact of using the wrong combination of screening and supplemental tests.

Then, when we converted to the Orgenon HTLV I/II test, we did do a significant change of a confirmatory algorithm, which I won't get into, but that has culled out the majority of false positives. So our rates now are getting back closer to what I believe baseline is here. But we still are seeing a high number of false positives.

Addressing specificity for HIV -- their initial and repeat reactive rates, which are shown on this slide since the implementation of testing in '85, have dramatically increased. And this graph only goes to 1995. But the performance of a combination assay has been very stable over time and through multiple publications has been shown to have excellent Group M sensitivity for HIV.

One additional HIV testing problem that Mike also referred to this morning that I'll talk about again is another kind of false positive we have in the HIV arena has to do with HIV 1 Western Blot false positives, and the 1993 Western Blot interpretive criteria change to exclude the requirement to have p31 to improve the sensitivity of the blot, which it did.

And if you look at a population of samples, which we did in a REDS study from my donor repository, we found 170 samples. And these were tested by RNA. And if you stratified them by the number of bands on Western Blots, you can see that the RNA positive samples in red -- the numbers increase as bands -- increase on blots as the presence of bands increase on the blots.

But those RNA negatives had few bands on blots. And, in fact, this entire category of envelope only did not contain a single RNA positive sample.

At this point, I also wanted to talk about the impact of p24 antigen screening on the blood supply, since it's part of the HIV menu, and it certainly has had an impact in specificity on what we do.

This slide was presented at AABB along with the whole presentation. But let me just summarize to say during two years of testing at the Red Cross for p24 antigen, which included 14 million donations, we have now had 136 samples that are confirmed HIV I p24 positive. But does that mean they are truly positive? No.

They sort basically into three categories. We have p24 antigen confirmed positives that are antibody positives. This is an expected finding. But we were detecting these anyway.

But we have a category here of false positives, which we didn't really understand would be a consequence of implementing the test. And our incidence of false positivity on the test is one in 250,000, and it was really quite a nightmare to cull out.

But there are a lot of data to show that absence of RNA, absence of reverse transcriptase activity, antibody negativity on followup and on index donation -- there is a wealth of data to show that these are false positive samples.

In addition, we've only had four now in 14 million donations who were recently infected seroconverting donors. And let me show that slide because it's probably the most relevant of all that

I have to show. These are the four positives, indicating, as Mike also did, how we stratify blood into our different regions.

So our first donor came from the southeast, male, 32, first-time donor, although he had attempted previous donation. No matter how many times we questioned this donor, no identified risk was identified.

The second donor used CUE, and Celso, in his previous talk, talked about the usefulness of CUE. Well, this donor did CUE. And this donor was a gay male who donated. He knew or was suspicious that he was positive, and that's why he CUE'd. The third one had sex with prostitutes from the southwest, and on repeated questioning or in followup questioning he didn't understand that having sex with prostitutes was an at-risk behavior.

And the last one here, which was not a Red Cross donor, was another male, 39. And again, through repeated questioning of this donor, there was no identified risk. So really, of these four, only 50 percent could we cull out a risk, one from a gay male and one sex with prostitutes.

So if we look at our overall yield at Red Cross, it has been one per seven million

screened, which I'll leave you to make your own conclusions about the efficacy of the test.

Okay. Another outcome of p24 antigen has been there is no interpretation of negative. If you are repeat reactive and you don't confirm, as with HBsAg, you're not called negative; you're called indeterminant, which is another set of unique nightmares.

But anyway, when we talk about donor reentry, I just want to use this slide which showed a PC -- a large study we did with REDS where we did PCR testing on about a thousand p24 antigen indeterminate donors. And in this test, we encouraged people to come back for followup sampling, so that they can be reinstated.

And at best on this test, which we do do an aggressive followup for, only 37 percent of donors come back. And of those, interestingly enough, 78 percent -- a vast majority -- remain repeat reactive.

Okay. So what now, talking about what we have, what contributes to false negative results? Certainly, the undetected infected individuals -- we have those within the window period because they are marker negative. We have a period referred to

immunosilence. There are viral variants. And, of course, there is test error.

Just talking about what we look at -- test error normally is reportable incidence through 483 observations or any category of reportable errors. There is also another category in here which never makes it to the FDA because there are errors that are found in-house by our quality control departments or quality assurance that don't allow the blood to ever leave the establishments.

And if a quality assurance episode is found, in most cases -- depending on what the nature is -- those are reported to the FDA. But this diagram perhaps disproportionately shows that non-detected or non-recorded incidence may occur, and we really don't know how many errors occur. And of those errors that do occur, how significant are they? How frequently do they occur in donors who are positive and would not otherwise be detected?

One way of showing these data are, again, to look through -- look at the PRISM clinical trials because they looked at an increased automated system relative to a system that -- the systems we use today that involve many, many manual steps of reagent preparation, plate setup, recording

expiration dates, manually reading results. So there are a number of manual steps.

But in the integrated clinical trials, they found 38, or 20 percent, of the failed runs were preventable technician errors. And although you can't read them, they're really mundane errors. They don't have any impact relative to safety, but if you look at these numbers -- 38, relative to the total clinical trial -- the number of preventable or technician errors totaled to .9 percent.

And even looking at retrospective records in my own laboratory, we know that with manual tests there's about a one percent error rate that is found by our QC or our other redundant laboratory record review processes.

So I wanted to leave the error message is that they may occur at a low level rate. We don't know how many impact true product safety, but certainly with systems in development we can look forward to addressing those.

Let me talk some about viral variants. The only reason I put this slide up is to remind myself to say that most of what we see in HCV is genotype 1; 75 percent of U.S. isolates are genotype 1. The first generation assays, which were

reported at about 70 percent sensitivity, had poorer detection of the other subtypes.

Second generation, or version 2, assays are stated to generally greater than 90 percent sensitivity, and the version 3 assays at greater than 95 percent sensitivity. And, really, the greatest impact that we're going to have on any changes in HCV will be with genome amplification testing, which I'll show some data for.

Relative to HIV, we know that we have a predominance of subtype B in the United States. In fact, studies that have compared different populations of U.S.-based individuals have shown that type B has predominated. These studies came predominantly out of Mike Busch's laboratory.

But recently, in the 1994/'95 CDC study donor base, and '95/'96, there was one each of a type A and one each of a type C. So pretty much we are not seeing the emergence of these variants in the United States.

Both of these had deferrable risks. They were recent immigrants from Central Africa, at least today's criteria.

And one thing I did want to show relative to variants for HIV are the numbers of HIV 2's that we've seen at the Red Cross since the

implementation of combination testing. Mike mentioned that there were two, and that's, in fact, true -- two of 37.5 million donations. So, again, like p24, or even worse than p24, a very low yield.

What we do in my lab is we test simultaneously by blot and HIV 2 EIA. So what we -- we have the unfortunate situation, if you will, is that we test a lot more samples for HIV 2 because we're also testing the positives.

Our first HIV 2 positive donor, though, was HIV 1 confirmed positive, albeit extremely weak profile on the Western Blot and having a much stronger HIV 2 profile. And this was published last year on transfusion.

Recently, a couple of months ago, we had another West African first-time donor who presented and was a strong HIV 2 positive donor who was only HIV 1 indeterminant on the licensed blot.

One way to address mutant -- excuse me -- variant detection for hepatitis B is to talk about the most common mutant that occurs in hepatitis B, which is the glycine-arginine substitution and amino acid 145. And of all mutants for hepatitis B, this accounts for about 75 percent of mutants. All of the individuals are core positive.

But just, again, to show you future developments in assays that will address mutant detection, if you look at an artificial construct of a mutant -- decreasing concentrations -- licensed assays may not pick up the sample. But on improved or enhanced versions of tests that improve HBsAg detection, they are readily detected.

Okay. And then focusing on the window periods, and then closing with some GAT testing information, we have really focused here on window period 2. If you look at from the time of exposure to infectivity, there is really an immunosilent period here, which I've called window period 1, which, according to classic virology, is referred to as the eclipse period.

And you can't detect if a person is infected. This is where a virus is replicating in the primary sites of infection. But once viremia has occurred, and we can detect viremic donors due to RNA and DNA assays, this is what we refer to window period 2 as.

One question is: are these viremic donations infectious? And then, lastly, if we have a non-viremic sample, would that donation be infectious? And there are studies trying to address those questions.

Okay. Just to look at risk -- this is from the Schreiber paper, looking at the window periods for the various agents and what we estimate risk at per million donations. How can we reduce this current risk?

And the obvious method here, as we've been talking about, is implementation of nucleic acid amplification testing, which -- and I think these are very conservative numbers. For each of these agents, you can see their projected window period reduction, what the relative risk would then be, and how much gain we're having over the total window period.

I've shown these slides at many meetings before, but let's just -- they are just serving to show you the window periods that we have with current tests. This is the antibody test. This is the antigen test. And then we have nucleic acid test. And you can really see that p24 antigen is a subset of the total RNA positive period.

And that positive period, if you put all of the data together, looking at the positive period prior to antigen, really, in these studies of 28 plasma donor panels, amounts to six days. So the window period from first RNA detection to first

antigen detection in these studies was only a six-day period of time.

Looking at HCV, viral titers are much higher and present earlier than they do for HIV. So the possibility of improving hepatitis C detection by doing RNA testing, rather than doing improvements in the antibody testing, is very promising, as we're all getting ready to implement GAT testing in the volunteer sector.

Looking at another profile, you can see the same thing here of RNA relative to serology. And in these studies, if you put all of the data together, looking at different periods of seroconversion, this just being the viral load, RNA positive, pre-antibody positive -- in these studies, we had a 41-day window period of RNA detection prior to antibody detection.

This study just shows a different population to TTVF study, and I got this slide from Mike. But one other benefit of doing the RNA testing here -- you can see the appearance of RNA in these transfusion recipients 12 days later after receiving the transfusion. This is their RNA positivity, followed by ALT, and, lastly, by EIA.

Well, the one nice thing that we should be focusing on when we implement GAT testing is the elimination of ALT.

Okay. The other point I wanted to make about HCV RNA, when we do get to GAT testing, is viral loads during the entire phase of infection with HCV are very high. So GAT testing should be very efficient.

Lastly, for HBV, in contrast, if you look at -- these are 28 seroconversion -- or, excuse me, 17 seroconversion panels. And this is EIA negativity followed by EIA positivity. And then, if you rerun these same samples by DNA, you can see that there is some period of time here, which in these panels amounts to 25 days prior to seroconversion, where you can detect low levels of HBV DNA. And that's the major difference between HBV GAT testing and HCV GAT testing.

Although there is a window period, if you look at all of these profiles, HBsAg and HBV DNA are almost perfectly coincident, except for some very early samples here that have low viral copy number. Here is another series to show you the very same thing.

So pool testing, basically, which this line shows you, would not be very efficient for

doing HBV DNA. But we do have a window period here to address -- which in the earlier slide I showed you was 20 days, and in this slide, from this series, gives you about 10 days. So, again, HCV is the only one with a considerably longer window period.

And again, not to push the point, but we can certainly make great strides in HBsAg detection, which certainly would benefit us greater than implementing another pool test for DNA.

So lastly, addressing where we are today, the donor screening tests do perform very well. There are minor problems with specificity, with confirmatory test strategies, with detection of viral variants, but the manufacturers are addressing a new version test. But overall, with the addition of new tests such as GAT, additional sources of risk relative to window periods will virtually be on the way to being eliminated.

I mentioned enhancement of existing tests to address variant detection, subtypes, or HBsAg mutants. And certainly, we have great strides to make in error elimination by looking at increased automation. And I think that's where the burden of changing any donor questionnaires would come, and these really could be addressed at having more

sophisticated levels of automation that take the human error out of testing.

Thank you.

(Applause.)

DR. DAYTON: And last but not least, we have Sue Preston, talking on PCR testing and narrowing of the window period.

DR. PRESTON: Good afternoon to all of you, and I appreciate the invitation to speak to you today.

As Mike Dubinsky and Joe get our overheads set up -- my name is Sue Preston. I'm with Alpha Therapeutic Corporation, and I would like to discuss the potential impact of gene amplification testing for HIV and HCV RNA on the safety margin for plasma derivative products.

Alpha Therapeutic Corporation has been one of the principal investigators on two investigational new drug applications sponsored by National Genetics Institute to explore the applicability of testing pooled samples of donation for HIV and HCV RNA.

The next few slides will depict the preliminary analysis of our clinical trial experience. I will then describe our post-clinical trial experience with continued testing for HCV RNA,

and, finally, I will discuss the impact of PCR testing on reducing the number of window period units that may inadvertently enter a plasma pool for manufacturing therapeutic products.

The IND sets forth a minimum of 300,000 donations from at least 10,000 donors for testing. Part of the investigation plan was to follow eligible subjects to seroconversion. The clinical trial was designed to identify the PCR positive donor as early in the donation as possible. Any donor that was positive for HCV RNA and negative for HCV antibody, as determined by the Ortho 3.0 ELISA, was asked to enroll in the followup clinical trial.

ALT testing was routinely performed for all donations with the Genetic Systems test, and all donations were tested for the absence of HBsAg, with the Genetic Systems 2.0 EIA.

Once enrolled, the donor was asked for a sample to test for HCV RNA and HCV antibody weekly for six months or until seroconversion. The clinical trial for confirming the HIV RNA positive donors had eligibility criteria for the subjects to include positive HIV RNA and/or reactive HIV p24 antigen test results, with the Coulter HIV p24 antigen ELISA; also, positive neutralization with

Coulter and nonreactive for HIV 1/2 antibody with Genetic Systems' second generation test kit.

When appropriate, the Cambridge Western Blot test kit was utilized to confirm repeatedly reactive antibody samples.

Next slide?

Each donation sample is represented in one layer, row, and column, and we employ this matrix to allow for rapid confirmation of a suspect positive individual through triangulation. This allows us to confirm a positive donor in three rounds of testing. Aliquots from the samples were combined into a 512 cubic matrix for PCR testing.

During the clinical trial, most of the samples from first-time or applicant donors were subjected to PCR testing only if the samples were negative for all other currently-licensed viral marker tests. However, for qualified or repeat donors, the PCR testing was conducted concurrently with the viral marker testing.

The pooled samples, and not more than 512 matrix, are sent to National Genetics Institute where polymerase chain reaction testing is performed for HIV and HCV genome sequences in separate reactions. And then the results are returned to our Memphis laboratory for correlation with other test

results and disposition of the individual units of plasma.

Next slide?

The investigational new drug application was submitted on February 17, 1997, and was approved by the FDA on April 30, 1997. Samples from each donation collected from 33 of our licensed sites were sent to our central testing laboratory in Memphis for PCR testing during the clinical trial of four months in 1997. During that time, 342,714 donations were tested.

In the HCV clinical trial, 22 donors were eligible to be enrolled in the study, of which 13 were successfully enrolled. In the HIV clinical trial, four donors were eligible to be enrolled in the study, and two were successfully enrolled.

Test data obtained from all eligible donors have been evaluated, and these results are presented in the next overhead.

This is HCV. The results of PCR testing in the 512 matrix are striking for the HCV RNA detection. Each of the 22 donors identified in the positive donations is represented by a bar going across. On the right side, the PCR positive donations are plotted from day zero, as the first positive PCR result, and they are depicted in blue.

Each of the tick marks represents a sample or donation.

PCR and HCV antibody positive donations are indicated in the yellow -- in the red color -- sorry -- on this one. And there is one sample that has a blue -- yeah, is antibody positive and PCR negative. And we think this may reflect the five to 15 percent of the HCV viremic individuals that clear virus what remain antibody positive.

On the left side of the graph, we have a series of donations prior to the PCR positive donation. The series in green indicate PCR negative and antibody nonreactive results. The gray bars represent samples from donations that were not subjected to PCR testing but were found nonreactive for HCV antibody. The seroconversion period ranged from 20 to 120 days, with a mean of 67 days and a median of 56 days.

What is significant is the number of potential window period donations that can be interdicted with PCR testing of pooled samples.

Next overhead?

This overhead depicts the seroconversion for the four donors identified as positive for HIV RNA. On the right side of the chart, the blue color denotes PCR positive samples. The yellow color

represents both PCR positive and p24 antigen positive samples, and the red color indicates positive results for all three HIV marker tests. That is, PCR, p24, and antibody.

We've plotted the results to show the first PCR donation on day zero, as we did in the first graph. And on the left side, we show the negative PCR results prior to the first donation where they become positive. And all of those donations have been tested with PCR as well as with antibody.

The lower two bars on this graph represent donors that did not enroll in the study and for whom we do not have samples to show antibody seroconversion. The upper two bars represent the enrolled donors. The data presented here are consistent with the published literature for a window period of approximately 20 days for antibody seroconversion and approximately six days for p24 antigen positivity.

It's significant that PCR in our matrix of samples could detect window period donations before p24 antigen testing in all cases. As of today, in our clinical trial we have not found a confirmed anti-HIV 1/2 or p24 antigen positive

sample that, if tested by PCR, is not found positive for HIV RNA.

So, in conclusion, even with HIV where we have a relatively short window period, PCR of pooled samples appears to allow earlier detection of window period donations.

This overhead shows the units that are interdicted only by PCR pool testing. In other words, they were not positive for antibody, nor were they positive for any of the antigen testing. During the clinical trial period of four months, 75 donations of source plasma were found to contain HCV RNA that were interdicted. Without PCR testing, each of these units would have been qualified for further manufacture.

Since the completion of the clinical trial, Alpha has continued to test our source plasma donations for HCV RNA, and an additional 373 window period units have been detected. During the clinical trial period, six HIV window period donations were detected positive for HIV RNA when all other test methods, including p24 testing, had failed to detect these units.

We then did some studies on some panels of our seroconverters and looked at these head to head with NGI's HIV qualitative PCR test to evaluate

the p24. And I think if you move it up a little bit. Each sample was tested with both the Coulter and the Abbott p24 test. And when either test was positive, the sample was considered positive.

In every instance, the p24 antigen was positive. The sample was also positive for HIV RNA by PCR when tested in a pool of 512 samples. In an additional 32 samples that were not positive for p24 antigen, HIV RNA was also detected.

Of the 71 samples -- negative donations, in this box -- of the 71 samples that were negative for both p24 antigen and PCR in the 512 sample pool, 22 of those donations tested positive at the single donation level with NGI's PCR test for HIV. And this indicates that there is still an opportunity for us to close this window even further as we get more and more sensitive test methods.

Next overhead?

Since the introduction of HCV RNA and PCR testing, we have observed a decrease in the rate of antibody positive donations. We have two graphs here. I'll talk about the upper one first. That is from the applicant donors. And the vertical red line, the first vertical red line, was in June '97, which is the time that we started our clinical trial. The second vertical red line over here is

when we had completed getting 100 percent of our donor centers on to the PCR testing protocol.

The June timeframe -- or the July timeframe was also the same time that we implemented the applicant donor program, where, as Toby Simon described earlier, we needed to have two donations where -- or two times when a donor had come in and was tested negative for all viral markers.

And we can see that the antibody positive donations for applicant donors decreased about 60 percent during that timeframe. For the qualified donors, which is a much different scale -- very low -- the rate has decreased approximately six-fold from .03 percent prior to PCR implementation to now .005 percent. And in the green is the confirmed positive rate, which is even 10-fold lower in terms of the rate.

If I can have the next overhead, the final overhead?

So, in conclusion, we believe that there are benefits to PCR testing to help with donor safety. The pool testing does decrease the viral load in the manufacturing pool by allowing the interdiction of units in the window period.

PCR pool testing does provide an opportunity for an infected donor to seek earlier

treatment. And for the HIV RNA PCR, we believe that it's at least as effective as p24 antigen testing in detecting pre-antibody seroconversion periods, source plasma donors.

Thank you.

(Applause.)

DR. DAYTON: At this point, I think we can combine questions with a panel discussion. I'd like to invite all of the speakers who have spoken since this morning's panel discussion to come up and join us in the front here.

Don't be shy, if you didn't get a card. I don't think there is anything intended by that. I think -- I'm not quite sure what went into that. But please come up.

I suppose we can start out by asking if there are any questions from the floor really related in any way to any of the topics we've been discussing today.

DR. RUTA: There's a lot of data to go over. Celso, I had a question for you. I think you showed 0.2 percent of people who come in to donate self-deferred because of the high-risk criteria. So about a quarter. Is that --

DR. BIANCO: That is correct.

DR. RUTA: -- a 20 percent deferred -- were deferred for other reasons? Those are temporary deferrals, the other reasons? Do those people come back?

DR. BIANCO: I did not try to separate permanent deferrals from temporary deferrals.

DR. RUTA: I thought you had some based on hemoglobin or some --

DR. BIANCO: That is correct.

DR. RUTA: -- other reasons. Do those people come back and --

DR. BIANCO: Yes, they come back. Hemoglobin, for instance, they'll come back. We'll encourage them to eat spinach and come back.

(Laughter.)

But yes, most of them are deferrals that -- but many of them are permanent deferrals, people that have cancer, people that are continuously on certain types of medication, people that have heart disease, and they will not come back. They will be permanently deferred.

So most of them I did not separate like that. I can do that. But many of them are permanent deferrals.

DR. RUTA: Yeah. I'd be curious about what percent of individuals who come in to donate

actually get deferred for permanent, you know, deferral criteria.

DR. BIANCO: It's a tremendous attrition, and it's a tremendous effort -- that is, to bring these donors up, and then many of them do not qualify, except for the hemoglobin. Even hemoglobin, a substantial number of them, particularly women, they are in a borderline, and that never reach a steady state to the point where they can donate at 12.5 grams of hemoglobin.

DR. RUTA: I guess we can ask the general questions.

But before we do that, I thought -- do people -- you know, does the data show that the deferral criteria for IV drug users, MSMs, people who exchange sex for money or drugs, are having an impact on the prevalence rate in first-time donors in the -- say, with the volunteer setting?

Mike, can I get you to --

DR. BUSCH: I mean, there's no doubt that the prevalence in the donor pool is, you know, two logs lower than -- in the first-time donor pool, two logs lower than what probably would be estimates of general population prevalence for HIV, HTLV. There is some reduction for HBV, and there is just

really a fairly modest -- maybe 10-fold lower -- prevalence for HCV.

In HCV, we run, you know, .3, .4 percent of first-time donors are confirmed positive compared to a population prevalence of maybe two percent. So much more modest effect in that setting.

And, you know, presumably that's attributable to the exclusion of these risk groups in which the prevalence is, you know, much, much higher.

DR. RUTA: Alan?

DR. ALAN WILLIAMS: I think one can make a similar argument for the prevalence of risk factors independent of the testing results. I think typically we find that in first-time donors and/or the overall donor pool that level of risk is about 10 percent what it is in the general population.

I know in one of the earlier talks today -- I think the hepatitis talk -- they used the blood donor survey data as the lower end of general population prevalence. But that really isn't appropriate because donors are high prescreened. And for most markers, risk appears to be about one-tenth, showing that there is considerable value to the current screening questions.

DR. RUTA: Well, let me ask you, since you raised the point, do you have -- or does anyone have suggestions on how one might improve the questions based -- and I'm asking you because of the data that you've gathered showing that people, you know, don't give accurate responses up front, but on secondary questioning of, you know, positive donors or through the mailers, then, you know, you can elicit correct or accurate responses afterwards. Are there suggestions for how --

DR. BIANCO: Martin, before we get there, I think that I'd like us to size a little bit the whole issue. The answer that Mike gave, I think, is accurate. That is, we have to attribute -- but it's not just medical history. It is not just questions. There is a whole educational program that goes on, at least that we try to do.

When we run drives in corporations, schools, churches, we give little cards that say, "If you have been exposed to hepatitis, or something like that, you should not donate." So there are several levels of screening -- people are aware of it -- that occur prior to the medical history.

So I don't know even if with current tools and with what we know we can precisely measure what is true to medical history. And the best that

I think that we can get is the change that we see when we added direct questions, because it was over a background within the medical history.

And I think that that was very positive, that was very clear. But I believe that at one point -- I don't know if it is to modify to improve the questions, but, again, it's to go back and ask, what would be the impact of each one of the changes? Do we have data to show that changing, for instance, 1977, or changing one of these groups -- IDUs or something like that -- what kind of impact it would have.

And Dr. Doll, I think, is the one that -- I don't know if I agree with your figures, but I think that you are the one that came the closest to trying to answer those questions.

DR. SIMON: Well, one thing I think that there has been a paucity of research in this area. We really -- one is almost hesitant to admit that we've never validated the questionnaire in the way we validate other things that we're required to do as a part of our processes.

And so I think that some kind of a structured research or validation of the questions would be useful. Whether it would be cost effective

or not, I suppose one could argue, given the current rates.

I think it is interesting if I -- and Mike Busch may want to comment on this further. I believe that almost the best data we have is despite the testimony of plaintiff's witnesses, it was in the '83 timeframe when we put in, the very first thing, the transfusion safety data -- showed this nice reduction in percentage in the San Francisco area, if I recall correctly.

So at least there is some data that introducing questions historically made a very significant reduction in risk. But it seems to me data is missing on whether our approach now is making any further reductions.

DR. BUSCH: Yeah. You know, there's no doubt -- before we had the screening test for hepatitis and for HIV, these risk deferrals were incredibly important and effective in preventing transmissions. The question now is, in the context of the accurate screening test, how much residual value they have.

And one of the things I think we saw today is there are studies in place now that are really measuring the incidence and prevalence accurately. And I think within those contexts,

there is the opportunity to do studies to explore alternative question strategies. And whether -- you know, FDA has to be willing to allow that.

It doesn't do any good to have to ask the old questions plus the new questions, because the old questions encompass the new options. But if in the context of some blood centers that are involved in these very carefully monitored donor bases, we examine alternative question strategies. And I think Lynda's analysis is right, given her assumptions, that the prevalence will go up.

But the question that intrigues me is whether we could actually have an offsetting -- you know, the prevalence goes up, if the tests work fine, no big deal, no problem. Maybe we need to add some second testing options.

But the other, you know, potential benefit is if we can focus people on the recent risk behavior, then, you know, would there be an offset that would more than outweigh any effect of increasing prevalence in test error on prevalence, with respect to interdiction of focusing people on their recent behavior?

I don't know whether there is any behavioral literature that would suggest that that's a reasonable promise.

DR. DOLL: It's hard to say, Mike. You know, there are at least some data that suggest that people will admit to older risks but are less likely to admit to more recent risk. So, you know, that would be counter to your argument, that focusing folks on their risk would be beneficial.

One of the things I guess I could mention, just to -- because several of you have asked about the prevalence figures -- if we look at the number of men who have sex with men, who might end up donating if we went to a one-year donation criteria, that figure is around 130,000.

And if we assume that -- if you look at the studies of gay men today, you assume that about a third of those men are engaging in risk behavior right now. And, in fact, there are some new studies that seem to be suggesting -- that is, by engaging in risk behavior -- that is, they're having unprotected anal sex.

There are at least some studies suggesting that the risk behaviors in that population is actually rising. And not only the risk behaviors, but there are some data on gonorrhea rates going up as well. So, you know, that's another level of data that we have not discussed here today.

When I presented my data, I presented data of men who had same sex partners. But we could take it to a different level and say, how many of these folks are actually engaging in risk behaviors? And what does that represent?

And, you know, my fear -- and I can best represent the data from MSMs -- and that is that those risk behaviors have gone up slightly lately. And --

DR. BIANCO: But what would make you decide to place them into the group that answers the questions truthfully or doesn't answer the questions truthfully? Because I think that that is the critical part, that we know that this type of -- we see from the vaccine studies how the young gay men are really ignoring the impact that HIV had in the older generation.

DR. DOLL: Exactly.

DR. BIANCO: But how do we know how they are going to answer the questions one way or the other? Because our decisions here are more about the questions.

DR. DOLL: Certainly. And my concern would be that they wouldn't, because it would be recent risk. Particularly if they are younger people, that they would deny their risk. That they

have a variety of justifications or reasons why they think their particular behavior may not be at risk, even though intellectually they understand that this behavior in men is a problem.

DR. RUTA: I think there has been some discussion, but just to read again the first two questions, just so we have it on the record. In the face of sensitive tests for HIV, HBV, HCV, and HTLV, should a) men who have had sex with another man, even one time since 1977, b) people who have had sex for money or drugs since 1977, or c) people who have ever abused intravenous drugs, and/or d) partners of the above, be deferred for life?

And the second question, which I think there has been some discussion already, is, what lessons have we learned from prevalence and incidence of HIV, HBV, HCV, and HTLV, in individuals who engage in these activities, with regard to blood safety?

I'm going to go ahead and finish it up. And the third one is, what lessons have we learned from emerging infectious diseases in individuals who engage in these activities with regard to blood safety? And if you --

DR. BIANCO: Oh, you want answers?

(Laughter.)

I'll try. I think that we learned today starting that from a point of view of -- I think that Mike said that we have a lot of tools to monitor incidence and prevalence. I think that we do not have the data to justify the exclusion of men who have had sex with men until back to 1977, on the sense that the benefits of '77 or those dates is not clear to me.

I think that it's clear that recent behavior, like one year, is something that we should address. I think it is also clear, in my mind, that, like in the discussion that we just had with Lynda, that the young gay men that are being identified in the HIV vaccine trials is an individual that, in theory, represents a risk to the blood supply because many of them are not aware of the risks that they pose to other people in society.

And that maybe those programs -- I know they include a substantial educational component. But maybe the blood donor side should be put in big letters there in those programs.

I think that what we also learned is that the IDU -- at least for me, that the IDU represents a more important means of thinking of both emerging diseases and in the infections here, and a more difficult problem to deal with.

And the last one was, what did we learn about emerging infections? I think that that's a little bit less clear. But I think that we learned that what we have in place is not sufficient, but there isn't much more that we can do to address it, except to keep our eyes open.

The observation that was made before here, that it took us more than five years to realize that the HIV represented a rather serious epidemic.

DR. RUTA: Sue, I have --

DR. STRAMER: Yes?

DR. RUTA: Actually, the other Sue. Sorry.

DR. STRAMER: Okay. That's fine.

DR. RUTA: I had a question for you. I saw on the data you showed a decrease in the hepatitis C antibody, you know, positivity in both applicant and qualified donors. If you take the PCR positives into account, are we seeing a general down trend in applicant and qualified donors who are positive by the sum of the two markers?

DR. PRESTON: I think certainly for the qualified donors we are seeing that. The applicant donors, I'm not so sure that that wasn't really a representation of the applicant donor program being

implemented at the very same time, because the applicant donors actually get tested for all of the viral markers prior to getting PCR screened, where the qualified donors are tested concurrently with the viral markers.

DR. RUTA: Would anyone else like to ask any questions or make comments?

DR. ALAN WILLIAMS: Just one comment relating to the questionnaire, and that is to compare the rigor with which the regulatory agencies apply to a laboratory test that is not there with respect to applying a new screening question to the universal questionnaire, to take, for example, the questionnaires about self or family experience with Creuzfeldt-Jakob disease, Babesiosis, and Chagas disease.

One question that we had in this 1998 survey that I didn't go into was whether the donors understood this question. And combining those who didn't understand with those who didn't know if they understood or not, it's well over 50 percent for each of those questions. And I think that's a problem when you're depending on that for screening.

As far as emergent infections, I think one comment to make is that even if the benefit that we get out of improving screening questions today is

low or marginal in the face of our highly-sensitive test systems, just remember that we may, once again, be fully dependent on the questionnaire process for a new agent for which we don't have a genome or an immunological marker.

And I think it behooves us to put the best sophistication we can into creating those processes from a behavioral standpoint and doing the best job we can in screening.

DR. BIANCO: I think that what you said is very important, and I'd like to follow with a point about the computerized donor interview. I think that there is -- I think that Dr. Zuck made a beautiful presentation today. There is an incredible amount of evidence from many fields that -- psychological fields -- that computerized interviews overcome some issues of privacy and issues of concern, and that people talk to computers more freely than they talk to other people.

And I remember that the AIR, the second component of AIR, also developed a computerized interview, but it got stuck because we were not able to answer a question that I don't think we were able to answer in the next several years. That is, is it better or worse than the current questioning system?

And the reason we were unable to do it is because we don't know what the current questioning system is all about. And we don't have, really, numbers and hard data that can make it effectively comparable to anything else. So I think that we have to get into the year 2000, bite the bullet, and accept what seems to be logical evidence instead of relying exclusively on data.

We know that liking testimony -- that is, we resisted automation; we thought that everybody was going to be afraid of it or make mistakes. But actually, when we look back, people that were changing pipettes and doing like that were making many more mistakes than any automated system. And I think that -- I got very encouraged by that process, and I feel that it's not a very important thing that I'm taking home from here.

MR. MISWAS: Robin Miswas, FDA. A question for Sue Stramer.

Sue, you showed a lot of wonderful data. One thing, you know, I might have missed -- and that was, when you were showing the HBV DNA, you know, some sort of gain that you might get using HBV DNA in the window period before HBsAg, you know, is detectable, what about -- I might have missed something. What about HBV DNA for when HBsAg goes

away, and, you know, anti-core is there? Did you sort of look at that or --

DR. STRAMER: Well, in the present clinical trials, I showed the 6.8-day increase on the front end of the window period. There was also the 12.8-day increase on the back end, which is the anti-core positive period. All of those samples are also DNA positive.

So whether it's the front end window or the back end window --

MR. MISWAS: Or the back end. Right.

DR. STRAMER: Right. DNA and HBsAg profiles are virtually superimposable.

MR. MISWAS: But, no, after the HBsAg --

DR. STRAMER: Disappears.

MR. MISWAS: -- disappears --

DR. STRAMER: Is still waning DNA, lower levels albeit, but there is still DNA present in samples and have been shown in followup samples such as you're asking about.

MR. MISWAS: And when the HBsAg --

DR. STRAMER: It is declined and anti-core remains.

MR. MISWAS: -- completely undetectable.

DR. STRAMER: Right.

MR. MISWAS: HBV DNA is --

DR. STRAMER: Correct.

MR. MISWAS: -- undetectable. That's what I was getting at.

DR. STRAMER: Right. Right. And there have been immune complex disruption studies that have shown release of DNA. One study like that was presented last year at AABB. So the numbers are small, but those kinds of samples can be found and demonstrated. They are all core positive. As you said --

MR. MISWAS: Core positive and HBsAg negative.

DR. STRAMER: Negative. Right.

MR. MISWAS: Right. Okay. Thanks.

DR. ZUCK: Could I make a comment?

Celso, thank you for the endorsement, I guess.

There's a fundamental difference between the AIR study, which a lot of people in this room are familiar with, and from the study that we are proposing to do at Hoxworth and at other centers. And that is that the questions that were asked in the AIR study were different than the questions that were asked by the local donor, by the local blood center.

So you really -- the Blood Products Advisory Committee had this awful problem of trying to compare apples to oranges, and they believed that there was more power in interactive video because all of the literature says there is. But we haven't proven it for blood donors yet.

So the flaws that you were alluding to in the AIR study we have tried to eliminate because identicals are -- the questions are identical to the way they are asked, either orally or through the video screen.

DR. EPSTEIN: Epstein, FDA. Yeah, I was going to make a similar comment. FDA is not looking for validation of the automated system in terms of prevention end points; only whether it delivers comparable information, and, of course, meets its specifications. We've crossed that bridge once.

The question I wanted to raise for the committee -- the issue, as it has been posed, is whether we should or could eliminate certain lifetime deferrals. And underlying the concept of lifetime deferrals was the concept of ongoing risk, which was related to the concept of a lifestyle choice.

And underlying that concept is the notion that a person with a past history of a

certain behavior is, in fact, more likely to engage in that behavior again. And I don't think that we heard any data today that help us understand at the behavioral level whether that's true or not true.

Putting the issue another way, if we were to move from lifetime deferrals to a floating deferral of, say, one year, have you engaged in X behavior in the last year, the question that presents itself from a safety point of view is: what is the infectious incidence and prevalence in a cohort described that way? In other words, persons who have a lifetime history but would deny a recent risk.

And I guess we didn't hear data in that category because nobody has it. But it seems to me that that's the fundamental problem that FDA has in trying to grapple with the question.

So my question to you is: do you know of any data that would be helpful to us in that regard? And if you don't, what do you think we should do to try to go about it? In other words, is that the issue that we need to resolve in prospect?

Because the alternative to that is we potentially relax these deferral criteria. We allow in cohorts who would have a lifetime history but lack a recent history. And we will only discover

the incidence after we have allowed all of these donations, which is the thing we don't want to happen if, in fact, risk were to go up.

So I ask the group, you know, what are your thoughts? Is that the right question? And if it is, how would we get those data, short of allowing it to be an experiment done on the blood supply, which I think no one would endorse?

DR. BUSCH: Yeah. I think you -- you basically have dispensed with the issue of prevalence in test error, accepting that, and basically what you're saying is given a person historically had risk behavior in the past, and then has discontinued that behavior, one is, is that person more likely to revert to reexposing themselves to that behavior? And secondarily, are they going to deny that in the recent behavior? That denial is -- it's tough to get at.

One thought is, you know, we do have information on level of risk in our positive donors. And one thing I think we'll be able to refine in the very near future is the denied risk in the very recently infected donors, where we get -- now that we already have incorporated the data with the detuned assays, so we can look at, with HIV, the

risk behavior in very recently infected donors, and the level of denied risk in that group.

And with HCV, I think with all of these RNA tests we'll be picking up a fair number of window phase infections. And if we can focus good questionnaires at those people, we'll get the much more accurate data on risk behaviors in the recently infected subset, not, you know, sort of diluted out by these old risk behaviors. So that's one piece at least that I think we can refine.

DR. DOLL: Jay, I have a suggestion for a data source possibly. Joe Catania in San Francisco actually has a study of men who have sex with men from eight cities, and it is probably the only nationally representative study of gay men in those eight cities.

And it's a longitudinal study, so that he may well have -- and I know that he is in the process of analyzing those data right now, and it is prospective.

He will continue to follow this cohort of men from eight cities. And so that is one place in which you might be able to get some data that partially answers this question.

DR. BIANCO: And the other population that may be very interesting is the population that

Ken Clark was describing to us today, the HIV positive donors. They are people that went through the system. They were positive. And to ask if they were recent infections, or if they are just prevalent infections, that Lynda did.

DR. SIMON: But we should be able to get the flip side of that, as you had suggested, Celso, and that is we have a ready source of information in those who have been deferred, as you have with the CUEs. What are the questions -- what the tests are, and those who have been deferred.

MR. DODD: Roger Dodd, Red Cross. I think that there are at least two other countries that have stepped back from permanent deferral, Jay. I know that you don't like to use data from out of the country, but the experiences there, I think, of Australia and the Netherlands, for example, may at least have some pointers if anybody has been able to analyze outcomes or look for step functions in test results. So it's not a unique situation.

DR. BUSCH: And thinking in the same way as Lynda kind of derived the proportion of, let's say, male sex male or IDUs who might come into the blood supply were we to relax the recent deferral. And then one could apply to that some prevalence rate, and then some test error rate, to estimate how

much test error occurring on prevalent infections would sneak in.

And you could potentially extend that to this issue. If you've got so many, let's say, persons who had a remote history of injection drug use, I would suspect CDC had some estimate as to with what frequency will these people revert. There may be some way to get at data in terms of reverting to that behavior.

And then we know from our data already with what frequency do people with certain behaviors in the donor base deny those behaviors and still donate. And, you know, from those kinds of sort of compounded models -- I mean, the problem is it's all models and it's all multiple layers of uncertainty on it. But we could probably get an estimate to Jay's question.

DR. DAYTON: Do we have any other comments or questions, either from --

DR. STRAMER: I guess my only question is: so I am operating with the underlying assumption that any increase in prevalence or incidence is unacceptable. And with any increase in incidence or prevalence, if questions were to change, that would be an unacceptable outcome

because it would put too much burden on our testing systems, which now have increasing safety.

We're going to add another overlapping layer of testing, with genome amplification testing. As I tried to point out, with automated systems coming forward, for licensure, it will virtually eliminate human error with these systems, assuming these systems work. So I guess I'm asking the question that -- again, back to: any level of increase in prevalence or incidence is an unacceptable outcome?

DR. DAYTON: I'm not going to handle that question.

DR. STRAMER: Well, I mean, but isn't that what we're talking about? If we're looking for the numbers to say they're increasing, isn't, then, the logic that we can't change the questions, because we're putting too much burden on our testing system?

DR. DAYTON: Well, it's not that you can't put -- take any change. It's just, you know, you have to --

DR. STRAMER: So we could assume worst case now --

DR. DAYTON: We have to see what change it is. We need the numbers. And, you know, we have tried to analyze it that way.

This also brings up another --

DR. STRAMER: But you could take numbers now and assume worst case test error rates, worst case variant, or window periods, and you can come up with rates and might show that one slide that had those numbers. So even if you assume that we will burden the system with this, is that an unacceptable outcome?

DR. DAYTON: Well, I can't speak for the entire FDA. I mean, I don't have an answer.

DR. BUSCH: I don't think it's under the FDA's control. I think you stated at the beginning -- Congress and the public want zero risk tolerance. And, you know, we've seen how the plasma industry has had to add p24 antigen and a genome test, despite the fact there is essentially no transmission.

We saw how all of us kind of reacted to that little blip in the tail of HIV prevalence, which is trivial, but we all saw it and we said, "Oh, God, something is going on we don't understand. We've got to react to that." I mean, it's just

almost a subconscious fear of the backlash of any increase.

And I think you're right, Susan, you know, I think we're kidding ourselves if we think we're going to be able to do anything that will allow a measurable increase in prevalence or incidence in the donor base.

DR. STRAMER: And to turn it around, we really are adding a lot to our layers of safety.

DR. BIANCO: But my question to you: do you expect an increase in the prevalence? It's definite. How much?

DR. BUSCH: The prevalence -- the basic fact is if you're going to remove the long-time deferral, you're going to allow some level of prevalent infections to come in. Any of these modifications --

DR. BIANCO: Well, what is the reason you have to say that they'll go through, that they are not going to say that they are at risk?

DR. BUSCH: No. What I'm saying is if you relax the criteria and, for example, allow male-male sex or IDU greater than one or five years ago to be eligible, persons who had unknown prevalent infections will become eligible and, you know, should give -- and prevalence should go up.

I mean, but we shouldn't -- that's not necessarily a risk to the blood supply because those infections will be culled out. It may be offset, in fact, by if we can focus their attention on recent and we get rid of the recently infected through a window period. But that's what we can't measure.

DR. SIMON: Another way to look at Susan's question is, to what extent do we integrate safety and availability and look at both aspects of that? Because if one has a measurable but insignificant increase, but has an increase in availability, thereby the total result could be safer for the patient.

DR. STRAMER: But in reality, I don't think the yield of what we're doing is tremendous, at least from looking at Lynda's data.

DR. SIMON: Yeah.

DR. BIANCO: And in addition, Toby, the less available, the safer.

MR. MISWAS: I'd just like to bring up the point of, you know, acceptability of increase in prevalence or incidence, or lack of acceptance of it. You have to keep in mind that although testing is very thorough and very good, the tests are very good, and nucleic acid testing will be brought in,

you have to keep in mind that GMPs can always be -- can be a problem now and then.

DR. STRAMER: Testing GMPs in the volunteer sector? I guess I don't -- do you mean inactivation GMPs?

MR. MISWAS: No. I meant that, you know, testing in a particular center, under particular conditions, might not be optimal always.

DR. STRAMER: One could say they are never -- I mean, nothing is optimal. But, I mean, optimization occurs both with donor questioning, as Dr. Zuck pointed out, with improved automation in all arenas. And I think we're going to see a decrease in test errors as we improve levels of automation.

MR. MISWAS: I agree with you that it's improving, improving, improving. But I think under certain circumstances, under certain circumstances in a particular location, at a particular time, things can --

DR. STRAMER: Things happen.

MR. MISWAS: -- you know, not work out the way you want to. And, therefore, you know, one would want to keep rigorous questioning in place. That's where I'm coming from.

DR. ZUCK: I don't want to be silly, but every time we do something, whether it's approved donor questioning or tweaking a test a little bit, we haven't changed the prevalence of anything. All we've done is changed the prevalence of what we found.

So I don't see this tremendous argument about, well, we hunt for all of this stuff, and the change of the prevalence is bad, and we have bad public policy. We haven't changed a damn thing. We just found a few more.

DR. DAYTON: Did anyone have any other further comment?

Well, I guess we can declare the meeting closed for today. Thank you very much.

(Applause.)

(Whereupon, at 4:49 p.m., the proceedings in the foregoing matter went off the record.)