UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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BLOOD PRODUCTS ADVISORY COMMITTEE

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BLOOD DONOR SUITABILITY WORKSHOP:

DONOR HISTORY OF HEPATITIS

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Wednesday, July 21, 1999

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The workshop was held in the Main Auditorium, William H. Natcher Conference Center, Building 45, 45 Center Drive, National Institutes of Health, Bethesda, Maryland, Edward Tabor, M.D., presiding.

PRESENT:

EDWARD TABOR, M.D., FDA

JAY EPSTEIN, M.D., FDA

ROBIN BISWAS, M.D., FDA

CATHY CONRY-CANTILENA, M.D., NIH

IAN WILLIAMS, Ph.D., CDC

RAYMOND F. KOFF, M.D., University of Massachusetts

PRESENT (Continued):

JOHN TICEHURST, M.D., FDA

ADRIAN DI BISCEGLIE, M.D., St. Louis University

GAY TEGTMEIER, M.D., Community Blood Center of Kansas City, MO

REBECCA HALEY, M.D., American Red Cross

STEVEN KLEINMAN, M.D., AABB

CELSO BIANCO, M.D., America's Blood Centers

TOBY SIMON, M.D., ABRA

PATRICIA HEWITT, M.D., NBS (U.K.)

HARVEY ALTER, M.D.

STEVEN FEINSTONE, M.D.

C-O-N-T-E-N-T-S

C-O-N-T-E-N-T-S (Continued)

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

(8:30 a.m.)

DR. EPSTEIN: It's a pleasure for me to welcome all of you to this FDA scientific workshop on the donor history of hepatitis as an exclusion criterion for blood donation.

This workshop is part of an ongoing effort at FDA to update all of the regulations pertinent to blood. Updating of the blood regulations itself is part of a broader initiative which we call the blood action plan that was instituted in July of 1997 to address blood safety issues broadly, as well as communication of risks related to blood.

This workshop is one of a series of workshops that have occurred and will continue to occur to reexamine the scientific basis of current policies on donor suitability. We had our last workshop in November of 1998 where we reviewed the science related to the current deferral for persons, males, who admit to have sex with males since 1977.

And we also have the possibility of another follow-up workshop on donor suitability possibly in October of this year.

Now, our staff have provided a list of other workshops that are being organized by the Office of Blood Research and Review in 1999, and this was placed out on the table where you entered, but let me just note for those who didn't pick it up that we will be having a workshop in September, September 24th, on bacterial contamination of platelets; a one and a half day workshop on blood substitutes, September 27th-28th. On October 18th there will be a workshop on plasticizers as a safety issue in blood collection and storage. We have planned on October 25th the workshop on inactivation of plasma derivatives derived from nonhuman source.

As I mentioned, we may have a follow-up workshop on donor suitability in October, and we've scheduled a workshop on leukoreduction December 10th, and a status report on implementation issues related to nucleic acid testing on December 14th.

So I encourage you to pick up the sheet and decide which workshops are worth your while to participate in.

Now, the history of hepatitis as a donor exclusion criterion, I believe, dates back to 1958, prior to the discovery of Hepatitis B, and of

course, the importance was that it was a precautionary measure to try to reduce what was then a rather high incidence of post-transfusion hepatitis.

Dr. Biswas will be reviewing the history of regulatory policy since then as it relates to the exclusion.

I would only remark that it seems timely to reexamine the utility of this exclusion in the light of current scientific knowledge regarding the agents which cause post-transfusion hepatitis, as well as the screening tests that are now available to prevent it, particularly the enormous progress that has been made through screening for Hepatitis C infection and the coming availability of screening using nucleic acid technologies.

Fortunately at this time we benefit from strong scientific leadership in the hepatitis area. I would particularly note Dr. Tabor, Dr. Feinstone, and Blaine Hollinger, who chairs our Blood Products Advisory Committee.

And I would say that on the issue of hepatitis risk, we have for decades enjoyed excellent scientific support toward policy making.

Let me also commend Drs. Tabor and

Biswas for developing an exciting program on this topic, which is quite interesting, and I would encourage everyone to listen hard and contribute actively to the discussion so that FDA can take advantage of the best scientific thinking as we reexamine the issue.

So, again, a warm welcome, and let me then turn the program back to Dr. Tabor, who will be moderating our first session.

DR. TABOR: Thank you, Jay.

The first speaker will be Dr. Robin Biswas, the Chief of the Laboratory of Hepatitis, who will talk about the regulatory history and background of the exclusion of donors with a history of hepatitis.

Dr. Biswas.

DR. BISWAS: Good morning. I hope I can get the slides going here.

I will give you a presentation about the regulatory history and some of the background to the question that we will be talking about today.

Now, the regulations that preclude persons with a history of viral hepatitis from donating whole blood or source plasma are the two regulations that I have up here. This one, the one

on the left, is the regulation in regard to donors who donate whole blood and blood components for transfusion, and this one is for donors of plasma for further manufacture into plasma derivatives.

Now, at least since the early 1950s blood establishments have used a history of hepatitis criterion for determining donor suitability, and at least since the early 1960s -- could you sharpen that, please? -- at least since the early 1960s, blood establishments included a history of jaundice or yellow jaundice as it's sometimes called in questionnaires.

Now, at least since 1964, and as Dr. Epstein just said probably sine 1958, there was a history of viral hepatitis donor exclusion regulation in place. The point is that these questions and this regulation, these regulations were in place before there were any specific and sensitive tests for viral hepatitis.

Now, a great step forward took place in 1965 when the discovery of Australia antigen was announced. This Australia antigen, so called because it was found in the serum of an Australian aborigine, turned to be, in fact, what we now call today Hepatitis B surface antigen, which is the

external coat of the Hepatitis B virus.

In those days, these first experiments were all done with Agar gel diffusion, which came to be called first generation tests. However, it's interesting to note that it took another two or three years to associate the presence of Australia antigen with viral hepatitis. In this paper, they at first thought that it had something to do, it was a marker of leukemia.

Now, the important point is that in 1972, Hepatitis B surface antigen testing of blood using a licensed so-called second generation test was mandated by the FDA, and at that time that included counterimmunoelectrophoresis, which basically meant that you put a current across an Agar gel diffusion gel and included rheophoresis and complement fixation, which were around and had about the same sensitivity of the counterimmunoelectrophoresis test.

By the way, the counterimmunoelectrophoresis test was the first licensed test for HBsAg.

In 1975, HBsAg testing using so-called third generation tests was mandated by the FDA. At that time that included radioimmunoassays. Shortly

thereafter enzyme immunoassays were developed with similar sensitivity and specificity. However, of course, the enzyme immunoassays were a lot more convenient to use than the radioimmunoassays. You didn't have to mess around with radioactivity.

Just very briefly talk about the relative sensitivity of these tests. First generation test, the Agar gel diffusion was one. If you take that as one, then the second generation, so-called second generation tests were two to ten times more sensitive than this, and the third generation tests were 100 to 10,000 times, and I would say that today the tests sort of are more on this side.

So you can see the great increase at least in the Hepatitis B surface antigen test, and that's important to keep in mind.

In 1973 came the discovery of Hepatitis A by Dr. Steven Feinstone, who was then at the NIH and now with us. 1973 to 1980, there were the development of Hepatitis A tests. In the end these were licensed I think around 1979 or '80. Not licensed; these were approved as diagnostic assays.

The important point is that it led to in 1975 the recognition that about 90 percent of

transfusion transmitted hepatitis with neither A nor B, so named non-A/non-B Hepatitis, which we now know today is Hepatitis C.

Now, so at the beginning of the '80s, you had a situation where there were sensitive and specific tests for Hepatitis A and Hepatitis B. Hepatitis B was being tested for in the laboratories, and people were beginning to ask whether one really needed -- what to do about the regulations where you ask somebody if they had a hepatitis in the past because of these tests.

Well, BPAC, the Blood Products Advisory Committee, in 1982, discussed this question, and they recommended not deferring persons with a history of hepatitis before age 15 years or persons with a history of neonatal jaundice. Before age of 15 years, most of the hepatitis cases that occurs in children is Hepatitis A, and of course, persons with a history of neonatal jaundice has got nothing to do with viral hepatitis because it is, in fact, due to fetal hemoglobin breaking down a few days after birth and increasing the bilirubin.

Now, the next step is that in the mid-1980s, a couple more tests were introduced into blood banking. This was the anti-HBC test, the

antibody to Hepatitis B core antigen test, and the ALT test, the alanine aminotransferase test. Both of these tests are diagnostic tests approved by the FDA.

They were implemented by blood establishments. They were not -- it wasn't mandated by the FDA, and they were implemented by blood establishments as surrogates, so-called surrogate tests, for this non-A/non-B hepatitis, Hepatitis C, because tests in the mid to late '70s and the early '80s showed that the incidence, the incidence of transfusion transmitted hepatitis, non-A/non-B hepatitis, in recipients would be lowered if you implemented these tests.

Now, it's important to note that after these tests were implemented, in fact, there was a drop in post-transfusion hepatitis. However, one has to note that at that time donor selection became far more rigorous because of the AIDS epidemic, and so it's difficult nowadays to sort out how much effect, in fact, introduction of the surrogate tests had.

In 1990 came the introduction of screening tests for anti-HCV, and these few words sort of cover up a lot of work in the '80s. Seven,

eighty ASAGA (phonetic) carried out by Mike Haughton (phonetic) and colleagues at Chiron, with a lot of help from Dan Bradley at CDC. They cloned, as you know, the HCV virus, and tests were developed for antibody to HCV, and this was introduced, as I said, in 1990.

In 1991, anti-HBC screening tests which had been implemented since the mid-'80s was recommended by the FDA to reduce the incidence of transfusion transmitted Hepatitis B. This was done because studies had shown that anti-HBC positive blood that was negative Hepatitis B surface antigen was associated with very few cases of transfusion transmitted Hepatitis B.

In 1992, the Advisory Committee discussed the question again of the donor exclusion for history of hepatitis, and the result was that FDA recommended, based on the Advisory Committee recommendations that donors with a history of hepatitis before age 11 years not be excluded, and again, this was based on data that was presented by CDC at the Advisory Committee meeting that almost all, a lot of Hepatitis A in persons under age 11 was Hepatitis A.

Now, also in 1992, the Advisory

Committee, at a meeting, stated that test results in the absence of a clinical or medical diagnosis should not be interpreted as a history of viral hepatitis for the purposes of the regulations that I showed you at the beginning of my talk, these two regulations.

In 1993, the FDA recommendations clarified that a history of viral hepatitis means the occurrence of an episode of clinical symptomatic hepatitis.

Now, in 1995, the National Heart, Lung, and Blood Institute of the NIH convened a consensus development conference on infectious disease testing for blood transfusion, and the panel made the following recommendations.

They recommended that ALT testing should be discontinued. These are the two surrogate tests. ALT testing should be discontinued because there was now a sensitive and specific test for hepatitis non-A/non-B, in fact, Hepatitis C.

In regard to anti-HBC testing, they recommended that this testing should be continued because it may prevent some Hepatitis B virus transmission to recipient and because it may act as a surrogate marker for HIV.

Now, in regard to ALT testing, I should say that many establishments, blood establishments, in particular, source plasma establishments, did not -- still continued testing for ALT because -- and also some blood banks as well discontinued testing for ALT -- did not continue testing for ALT because of European plasma testing requirements.

So in 1995, FDA recommended that if, if a blood bank performs by choice ALT testing, units with a level that was more than two times the normal should not be transfused or used to make injectable products, and the products with levels of ALT more than two times normal should be labeled, should be so labeled.

Now, today donors of blood and blood components for transfusion tested for very sensitive HBSAG test, a sensitive anti-HBC test. There are problems; there have been some problems with specificity. Sensitive, specific anti-HCV tests, and some blood and blood components are, I believe, tested still for ALT.

Plasma for further manufacture into injectable products as far as viral hepatitis is concerned is tested for HBSAG, for anti-HCV and ALT. It's note tested for anti-HBC because if one

did test it and one withheld such units from the plasma pools from which plasma derivatives are manufactured, at the same time anti-HBS, the neutralizing antibody, would be -- the titres in the pools would diminish, and it is believed that anti-HBS content does contribute to the safety of plasma derivatives in regards to possible Hepatitis B virus contamination.

In addition, I should add here that, of course, all of these products, plasma derivatives, undergo validated viral inactivation and removal procedures.

In 1989, 1990, as Dr. Epstein just said, really we've seen the beginning of the application of nucleic acid detection tests, so-called NAD tests, for screening blood and plasma under INDs. Most of this as far as hepatitis is concerned is for Hepatitis C, and of course, it's done for HIV at the present time. Whether this will become universal for HBV remains to be seen.

But the point is that this NAD testing is expected to lower the already extremely low risk of donating an infection -- of using an infectious unit because the window period -- these tests will pick up infectious units in the window period prior

to the serologic test being positive.

To finish up, where are we today in regard to donors with a history of hepatitis? Today the following is what the policy is.

A donor with a history of clinical viral hepatitis after 11 years of age should be deferred. At present, viral hepatitis might include jaundice or a clinical diagnosis of hepatitis. In a donor with a history of jaundice, if it is not possible to rule out viral hepatitis as a cause of the jaundice, the donor should be deferred.

And lastly, I would say that the goal of the workshop today is to try and answer the question: is there sufficient information today to consider eliminating the exclusion of donors who have a history of viral hepatitis?

And thank you for your attention.

DR. TABOR: Thank you very much, Dr. Biswas.

I'll now talk to you a bit about some of the background of -- could you focus that, please, and maybe dim the lights slight? I'm going to talk to you a little bit about some of the early studies that were done on the use of the history of hepatitis as a donor screening question.

This is a question that has been with us for quite a long time, as Dr. Biswas explained to you. In fact, it has been the subject of major debates in public fora.

For instance, in 1982, June of 1982, it was brought to the Blood Products Advisory Committee, and the intention of bringing it to Blood Products Advisory, according to the written records, were to reexamine this exclusion "in the light of modern serologic capabilities."

Now, in 1982, "modern serologic capabilities" included sensitive third generation tests for Hepatitis B surface antigen; sensitive radioimmunoassays for antibody to the Hepatitis B core antigen, and although not applied to blood donation sensitive tests for anti-HBS.

The discovery of the Hepatitis A virus had taken place almost ten years before by Dr. Feinstone, and the sensitive test for detecting antibody to Hepatitis A virus were at that point moving out of the laboratory, out of the research laboratories and were becoming more generally available.

We do not have an existing transcript of this 1982 BPAC meeting, but we do have summary

minutes available.

And in 1982, just to give you an example of the way this subject was approached some time ago, the BPAC recommended, first of all, that the exclusion of donors with a history of hepatitis remain in place for those who had a history of post-transfusion hepatitis, that is, a history of hepatitis that occurred some time following a transfusion, or for those who had a history of hepatitis that was associated with intravenous drug use.

The BPAC in 1982 acknowledged that technologic developments in serologic detection had essentially superseded this question that had been put in place before the availability of tests, and they recommended, as Dr. Biswas pointed out, removing the exclusion for those with a history of neonatal jaundice or those with a history of hepatitis before age 15.

Now, the availability of the third generation, that is, the more sensitive test for the Hepatitis B surface antigen in the mid-1970s led the Food and Drug Administration, specifically the Bureau of Biologics, which was the forerunner of what we now know as CBER, to initiate a study

through a contract to evaluate the usefulness of this question, and this contract was awarded to the Red Cross. Serum samples and questionnaires were collected, and then they were both analyzed by the Red Cross and then completely reanalyzed in our laboratories at BOB.

When I first came to the Bureau of Biologics, it was not quite that early, but the contract was still in its early years, and I was given the assignment of directing that contract and doing the research.

The participants in that contract and in the studies were, in addition to myself, Dr. Hoffnagle, who's now at NIH but was at BOB at that time; Dr. Linda Smallwood, who was at BOB; Dr. Drucker, who is a visiting scientist at BOB; Dr. Pineda Tamandong, who was at the American Red Cross; Dr. Louisa Ni, who is still very active in the blood field and was at that time in the Red Cross; Dr. Greenwalt at the Red Cross; Dr. Barker, who was at FDA at that time, but later was at the Red Cross and is still very active in the field; Dr. Gerety at BOB; and Dr. Ryan Nath, who was at the Red Cross.

Now, the object of the study was to

collect about 3,000 sera from prospective blood donors, that is, donors who had not yet been screened by serologic tests, and the intention was to get approximately 1,000 units, 1,000 sera and questionnaires from donors with a history of hepatitis and no history of transfusion; 1,000 from donors with a history of transfusion and no history of hepatitis; and 1,000 from donors with no history of hepatitis and no history of transfusion.

And these studies resulted in two publications. The citations are shown here on this slide. They both appeared in Transfusion in 1979 and 1981, and because of the extra amount of time it would take any of you who are interested to find these in the library, we've included copies of these publications in your packet.

Well, the overall conclusions from these studies were as follows. First of all, in these studies HBV markers, that is HBV markers totally, Hepatitis B surface antigen and anti-HBC, anti-HBS were detected in a great number of donors with a history of hepatitis than in those with no history of hepatitis.

However, the only one of those markers that would be useful for screening for active

infection at that time was thought to be HBSAG, and HBSAG positive individuals would clearly be excluded by screening their sera at the time of donation.

But in looking at this data from the perspective of 1999, I think we have to ask the question is there any risk from anti-HBS positive donors, and I raise that question because of a paper that most of you are familiar with from Dr. Chizari's (phonetic) laboratory, the results of a study conducted by Dr. Chizari and Dr. Barbara Rahrman (phonetic) and others, which reported the detection of HBV DNA in anti-HBS positive individuals.

I'd like to emphasize that the infectivity of such samples has not been proven by any means, but it is a topic for discussion later in today's session.

In this study we also looked at donors who had anti-HBC alone, that is, no HBSAG detectable, no anti-HBS detectable, but anti-HBC detectable, and we found that anti-HBC alone was prevalent at a significantly higher level in donors with a history of hepatitis compared to those with no history of hepatitis, 2.6 percent compared to .4

percent. That was a highly significant difference.

And even though donors with a history of hepatitis who had anti-HBC alone had higher endpoint dilution titres of anti-HBC, that was not found to be present at a statistically significant level, and even though they more often had IgM anti-HBC, that too was not found at a statistically significant level.

So our conclusions with regard to anti-HBC was that even though anti-HBC was more prevalent in donors with a history of hepatitis, it really indicated that more of them had previously had Hepatitis B virus infection and presumably had recovered and not necessarily that they more often had current active infection.

Well, I'm going to just briefly show you some of the actual data so you can see what I'm talking about. We had 1,151 donors with a history of hepatitis. Looking at total HBV markers for HBSAG anti-HBC and anti-HBS, HBV serologic markers were found in 220, or 19 percent, and compared to those with no history of hepatitis in whom these markers were found at 6.3 percent, you can see that there's clearly a statistically significant difference in total HBV markers.

Breaking it down according to the markers, just looking first at HBSAG, it was found in one percent of those with a history of hepatitis. This is, of course, as I said before, before they donated, before their blood was collected. So obviously they would have been excluded by this test, and only in .2 percent of those with no history. This was a statistically significant difference.

I've already discussed the anti-core results, and anti-HBS was found in 15.6 percent of those with a history of hepatitis compared to only 5.8 percent of those with no history of hepatitis.

I think if you look at these numbers, you can see that that's clearly a statistically significant difference when you have such large denominators as are shown over here in the total number of patients in each group.

If you go to the paper itself, you may find the statement regarding statistical significance a little confusing because in the paper, we compared this figure, 15.6 percent, to the prevalence of anti-HBS in another group of donors outside of the ones that I've described to you so far, and I merely call that to your

attention in case you find that confusing if you look at the paper.

Now, another part of this contract was to collect sera and questionnaires from implicated blood donors, and these were blood donors who had donated blood and whose blood had been received by recipients of one or two unit transfusions. That is the recipients either got just this donor's blood or this donor's blood plus the blood from one other donor, and the recipient developed hepatitis.

In a large number of cases, the hepatitis was non-A/non-B hepatitis or what we now know as Hepatitis C virus, and as Dr. Biswas pointed out, about 90 percent of post-transfusion hepatitis in these years was due to non-A/non-B hepatitis.

In this part of the contract, we collected blood from 129 such implicated donors, and this is actually a very important historical event because two of these donors constituted two of the first four infectious inocula for the transmission of Hepatitis C virus of chimpanzees that were reported in back-to-back articles by our laboratory and Drs. Purcell and Alter (phonetic) in 1978.

And it was because of this study that we were able to obtain these samples and the development of the chimpanzee model, of course, made it possible for investigators at Chiron and the CDC to clone the Hepatitis C virus and develop a sensitive assay.

Well, among these 128 implicated donors, that is, 128 donors whose blood presumably in most cases had transmitted non-A/non-B hepatitis, none of them, none of the 128 had a history of having had clinically recognizable hepatitis. None of them were excluded by the question that we asked about whether you've had clinically recognizable hepatitis in the past even though markers of HBV were found in 23 percent of them and markers of Hepatitis A virus in 44 percent.

Now, they didn't all transmit hepatitis or non-A/non-B hepatitis because, as I said, these were one and two unit transfusions that were involved, but clearly a very large number of them had transmitted non-A/non-B hepatitis even though they had no history of clinically recognizable hepatitis.

So the conclusions of the studies conducted at Bureau of Biologics of CBER were as

follows. The studies concluded that a history of hepatitis is not a useful screening question for non-A/non-B hepatitis because so many of the implicated donors had no history of clinical hepatitis.

We concluded that it was a useful screening test for Hepatitis B virus, recognizing however that HBSAG positive donors would be detected by serology.

Finally, the statement was made in one of the two publications and shown here in this side whether it would eliminate infectious units with HBSAG and low titres undetectable by RIA cannot be determined, and I think that's something we'll have to discuss today, and it's very relevant today, as well as it was at the time it was written.

The question is: can this donor question about a history of hepatitis detect those donors who either have long term, chronic Hepatitis B with undetectable HBSAG or can it detect donors who are in the window period who either would be detected by nucleic acid testing when that's fully in place or perhaps donors who might be missed by nucleic acid testing, although I think that's a little less likely?

I'd like to just point out that around the same time, an analysis was published by other investigators about the number of units of blood that would be affected by or that were being affected by or that were being affected by excluding donors with a history of hepatitis, and in that study they reported that .6 percent of prospective blood donors in the United States were being permanently deferred because of having had a history of clinically recognizable hepatitis, and this amounted to 56,000 donors per year.

Well, I think these early studies give us a good starting point for some of the clinical data that we're going to hear, and I think they're a good starting point for discussions about whether this question that we ask all donors has value in 1999.

Thank you.

The next speaker will be Cathy Cantilena from the Clinical Center at the National Institutes of Health, and she'll be going over the clinical aspects and viral markers of Hepatitis A, B, and C.

DR. CONRY-CANTILENA: Thanks, Dr. Tabor.

I have to figure out how this works here first.

Okay. Well, what I've been asked to speak about this morning is the very basic clinical and virologic serology of Hepatitis A, B, and C. So this is maybe a blast from the past for a lot of you who went to medical school and grad. school. So I guess I'm apologizing in advance for its basicness.

Drs. Biswas and Tabor nicely reviewed what the FDA perspective on deferral of donors was. What I'm giving you here is what the AABB standard is for donor deferral for those who present with a history of hepatitis, and that is that prospective donors shall be indefinitely deferred from donating blood components for transfusion who have a history of viral hepatitis after their 11th birthday or who have had a confirmed positive test for HBSAG or a repeatably reactive test for anti-Hepatitis B core on more than one occasion.

What I'm going to speak about today a little bit is the virology, and I've purposely, although I'd like to talk about epidemiology I won't because Dr. Ian Williams will follow me and, I hope, talk about risk factors and transmission and such thing.

I will talk about the clinical and lab

features, serologic diagnosis, any atypical courses associated with Hepatitises A, B, and C, and briefly mention treatment prophylaxis and prevention of these viruses.

To begin with Hepatitis A, Hepatitis A virus causes acute hepatitis and is still a major problem in some underdeveloped countries worldwide. It is a positively single stranded RNA virus without a lipid envelope of approximately 7,500 nucleotides. It has four stable human genotypes, and its vaccine protects against all of these strains.

After oral inoculation, it is taken up by hepatocytes, and the liver is the only target organ for injury, and it replicates in the cytoplasm of the hepatocyte.

From the liver it's transported back through the biliary tree to the intestine where it's shed in the feces.

These are the clinical features that are really common to all types of hepatitis, but more specifically for Hepatitis A virus I've included here a prodrome which may include fever, malaise, weakness, nausea, vomiting, and in children may present with some flu-like symptoms. With

hepatitis there is an association of dark urine and a mild pruritus, or itching; jaundice, yellowing of the eyes and skin; perhaps mild hepatomegaly; and Hepatitis A virus ALT of the transaminase elevations that you'll usually see are generally routine 500 and 5,000 international units per liter, and the bilirubin, the total bilirubin does generally not exceed 171 micromoles per liter.

These are the clinical features that I've listed here for Hepatitis A virus. The incubation period of Hepatitis A virus is about 15 to 50 days, with a mean of about 30 days. Hepatitis A is excreted in the feces for one to two weeks before the onset of illness and about 18 days afterwards.

Fecal oral transmission is the predominant way of spreading Hepatitis A virus. Sequential infections do occur about one incubation period apart. Usually Hepatitis A virus affects children without producing symptoms, but in adults it causes clinical apparent disease, often with jaundice.

Jaundice develops in 70 to 80 percent of adults and in less than ten percent of children. There is increased clinical severity of Hepatitis A

virus with age. It is not linked to chronic liver disease, persistent viremia, or an intestinal carrier state. Most patients show complete clinical and biochemical recovery within three to six months.

There are three atypical courses that are recognized, which included fulminant hepatitis or acute liver failure; cholestatic hepatitis; and relapsing Hepatitis A. However, the prognosis for complete resolution, that is, absence of chronic infection if one lives through the syndromes, is excellent.

Hepatitis A is differentiated from other forms of acute hepatitis by serologic testing. The diagnosis depends on finding IgM HAV antibody during the acute phase of illness. IgM persists for three to six months afterwards. Positive tests for total anti-HAV without IgM anti-HAV indicate the presence of IgG and HAV. IgG alone indicates past infection.

There are few published data regarding the continuity of viremia and the clinical conditions in Hepatitis A infection. In one study which looked at 25 Hepatitis A virus patients, the mean duration from the onset of clinical illness to

the time HAV RNA was lost from serum was a mean of 18 days plus or minus 14 days into the convalescent phase.

This presents a diagnostic profile of Hepatitis A virus infection. After exposure, HAV shedding in stool is present at about seven to ten days, although the exact time line is not given along the X axis. And this is about one to two weeks before symptoms appear.

Though the ALT curve is not shown here, fecal excretion of HAV continues as the ALT rises. Symptoms appear generally about one month after exposure. Hepatitis A virus excretion begins to diminish and anti-HAV appears.

Although IgG anti-HAV may be present early in infection, it is always accompanied by IgM at the onset of illness. As IgM diminishes three to six months after, IgG persists and it reflects recovery and resistance to further infections.

There is no specific therapy proven effective for HAV, and treatment is supported with hydration and rest. The passive immunization, as far as prevention and prophylaxis go, passive immunization with IMIG, or intramuscular immune globulin, containing HAV IgG has been the mainstay

of prophylaxis for about 50 years, even before protective antibody was serologically defined and before vaccines were available.

It is still used for post-exposure prophylaxis of household contacts of affected individuals. It may not be effective if it's given more than two weeks after exposure.

The duration of protection with IMIG is dose dependent and short, and is generally no more than four to six months.

Several inactivated vaccines are now available, and the first was approved in the United States in 1995. They are whole virus preparations that are inactivated with formaldehyde and are generally well tolerated.

After IM inoculation of two doses of serum concentrations of anti-HAV approach those of natural infection and are detectable in serum as early as 15 days after a single dose of a vaccine in 70 to 98 percent of those who are vaccinated, and field studies for HAV vaccine have found a protective efficacy, cumulative rates of 90 to 100 percent.

Immunity from the vaccination is likely to last ten years.

What's new? Can you focus that a little bit for me? I don't think I have a focus button down here. Okay. Thank you.

In searching the literature to see what was new with Hepatitis A, I found two reports in the last couple of years that have drawn some attention to Hepatitis A virus, and they appeared in the Annals of Internal Medicine and the New England Journal of Medicine. They stress the serious side of Hepatitis A virus infection.

The first describes a group of patients that were hospitalized during a 1994 and 1995 epidemic in Tennessee, stressing that there was serious illness and death associated with acute infection, particularly in people who are older than 40 years old, and again, those who got over the disease were fully recovered.

And the second report described acute Hepatitis A virus, hepatitis in patients who had underlying Hepatitis B virus and C virus infections, and showed that most patients who had chronic Hepatitis B virus and acquired HAV had an uncomplicated course. However, the patients with chronic Hepatitis C virus had a substantial risk of fulminant hepatitis and death associated with the

Hepatitis A virus superinfection.

Transfusion associated Hepatitis A virus is such a rare event that blood donor serologic screening is not done. Adult donors are generally symptomatic of disease and not donating blood when they feel ill.

However, there have been reports in the medical literature of pooled blood products that do transmit or have transmitted Hepatitis A. Since it is a nonlipid envelope to virus, it's not inactivated by products that are treated with solvent detergent alone, and hemophiliacs in Europe and in the USA have been reported to acquire HAV infection after the contamination of the concentrate they had received did occur, and these were reported in Annals of Internal Medicine, Vox Sanguinis (phonetic), and the MMWR in the past five years.

Moving on to Hepatitis B, Hepatitis B is a partially double stranded, circular DNA virus, and it's a member of the hepadraviridae family. The virus consists of a central core nucleocapsid or the Hepatitis B core antigen that encloses the viral DNA.

Hepatitis Be antigen is a circulating

peptide that is derived from the core gene and serves as a marker of active viral replication in the serum. Serum Hepatitis B virus DNA is the best and most sensitive test to indicate active viral replication.

Hepatitis B surface antigen indicates -- is indicated here, and it is the surface or outer envelope antigen. Antibody to Hepatitis B surface antigen confers protective immunity.

These are some of the clinical features that I've illustrated for Hepatitis B virus. The clinical incubation period averages 60 to 90 days with a range of 45 to 180 days. The onset is often insidious. It is transmitted percutaneously, percumucosally, as well as perinatally.

Hepatitis B virus causes illness in 30 to 50 percent of individuals who are older than five years and in less than ten percent of individuals who are under five years of age.

The symptoms include anorexia, nausea, vomiting, abdominal pain, mild fever, and dark urine. Jaundice develops in about 25 to 35 percent of the patients who present with symptoms.

In contrast to Hepatitis A virus from which no chronic infection occurs, of those who are

acutely infected with Hepatitis B virus, 80 to 90 percent of infants, 30 to 50 percent of children under five, and five to ten percent of those older than five years old go on to have chronic infection. So the older one gets, the less likely that Hepatitis B virus will become chronic.

Among all age groups, 15 to 25 percent of those with chronic infection will die prematurely of their chronic liver disease.

I have enumerated here several of the clinical syndromes that have been associated with Hepatitis B virus, that is Hepatitis D, Hepatitis C virus, often a co-infection, as well as HIV, fulminant Hepatitis B virus, infection with mutant strains of the virus such as Hepatitis E antigen negative viruses.

There are extrahepatic diseases associated with Hepatitis B virus, as well, such as polyarteritis notosa (phonetic) and mimenoproliferative glomerital endofritis (phonetic), as well as hepatocellular carcinoma, and for the sake of time, I have just enumerated them for you here, and perhaps some of the other speakers will speak more about some of these problems.

I've go ahead here and defined the serology of Hepatitis B before I move on to what it looks like in terms of a diagnostic profile. Hepatitis B surface antigen, as I mentioned, is the viral envelope glycoprotein and the basis of the Hepatitis B vaccine. Anti-HBS is protective and neutralizing antibody, and it can become undetectable in persons who have fully recovered from disease.

Hepatitis B core antigen, again, the nucleocapsid enclosing viral DNA, the antibody to Hep. B core is present in all patients who have ever been exposed to Hepatitis B virus and is not protective. Its presence alone cannot be used to distinguish acute from chronic infection.

The different types of anti-Hep. B core that can be present at IgM, which is associate with acute infection, or flares of chronic disease, and the IgG antibody which persists for life after infection.

Hepatitis Be antigen is the circulating peptide from the core region, a marker of active viral replication, and present only in persons who have serum of Hepatitis B virus DNA, which is the best indicator of viral replication.

Antibody to Hepatitis Be antigen appears when the E antigen is cleared and the virus is no longer replicating.

Here is the first of two serologic time courses I want to show you. This reflects acute infection. The first serologic market of Hepatitis B virus infection following the exposure is Hepatitis B surface antigen. Though not presently used as blood bank screen tests, Hepatitis Be antigen, DNA polymerase and Hepatitis B virus DNA appear at the same time, at about the same time as Hepatitis B surface antigen, which is about 30 to 60 days after exposure.

The Hepatitis Be antigen in serum correlates with high titres of HBV and greater infectivity. ALT levels rise and peak at the time symptoms and jaundice are present. In persons who recover, Hepatitis B surface antigen is no longer detectable in serum after a period of about three months after the onset of illness.

A diagnosis of acute HBV infection can be made on the basis of IgM class antibody to Hepatitis B core antigen in serum. IgM to Hepatitis B core is generally detectable at the time of clinical onset and declines to

subdetectable within six months.

Anti-core IgG persists indefinitely as a market of past infection, but as I mentioned, is not a protective antibody. Anti-HBS becomes detectable during convalescence after the disappearance of Hepatitis B surface antigen in patients who do not progress to chronic infection.

The so-called window period of acute HBV infection is shown here and where the Hepatitis B surface antigen disappears, but anti-HBS has not yet become detectable. In this window, anti-Hepatitis B core is present. The presence of anti-Hepatitis BS, as mentioned, generally indicates recovery, and it is the sole marker of immunity after vaccination.

This slide illustrates chronic Hepatitis B virus infection. An individual is considered chronically infected if Hepatitis B surface antigen is present for more than six months. Hepatitis B surface antigen and anti-HIB core will be present.

Hepatitis Be antigen may or may not be present depending upon the stage of disease progression. Sometimes late in the chronic stages anti-Hepatitis B antibody will appear. There is a

conspicuous absence here of anti-Hepatitis B surface antibody.

The IgM anti-Hepatitis B core diminishes, but may appear during a flare of chronic illness later in chronic hepatitis.

The best serologic follow-up of patients who contracted Hepatitis B virus or at least the largest here occurred in the U.S. Army when recruits received a vaccination for yellow fever virus that was contaminated with Hepatitis B. The study of serology in follow-up was performed by Dr. Safe and his colleagues.

This serology shows that the group who had become symptomatic with Hepatitis B virus, in that group who was symptomatic only one went on to have chronic infection, and this is in nearly 600 Army recruits with follow-up many years later.

Ninety percent of these recovered having anti-Hepatitis B core and anti-Hepatitis B surface antigen. Seven percent of them had Hepatitis B surface -- anti-Hepatitis B core alone.

In the Group 2 here that you see, no one went on to have chronic infection. These were the gentlemen who did not develop symptoms. Most of them, 70 percent of them, had anti-Hep. B core and

anti-Hep. BS, and one percent had core alone, and six percent had anti-HBS alone.

The presence of anti-Hep. B. core could indicate the waning of detectable anti-HBS with time or the failure of anti-HBS antibodies to develop with low levels of Hepatitis B virus replication.

So in conclusion from the study, the Hepatitis B viral immunacy (phonetic) that was acquired was lifelong after they acquired natural infection, and there was a low Hepatitis B surface antigen carrier rate, only one in 348 among healthy young adult males who did acquire infection, although at that point in time there was no molecular testing that was done.

What could anti-Hepatitis B core mean as the sole marker, as is used for Hepatitis B virus infection?

It could be a false positive enzyme immunoassay, given its low specificity in repeat blood donors, and that is perhaps the likeliest explanation for most blood donors.

It could also mean the loss of anti-HBS with time or the failure of anti-HBS to develop after infection.

Thirdly, it could represent the window phase of acute Hepatitis B virus infection after the HBS antigen disappears and before anti-HBS appears. It could also represent the HBV carrier state with undetectable Hepatitis B surface antigen and lower levels of HB virus replication.

I'm going to move on quickly through Hepatitis C now to finish up. Hepatitis C was first recognized as a separate disease entity in 1975 when the majority of cases of transfusion associated hepatitis were not found to be caused by the only two recognized viruses at the time, Hepatitis A and B. Thus, it was called the non-A/non-B virus.

In 1989, the cloning and sequencing of the virus was reported, and the virus at that point was renamed Hepatitis C.

Tests for antibody to Hepatitis C quickly followed, and screening for such antibody remains the mainstay of diagnosis.

I'm sure everyone has seen this slide many times before, and it illustrates the genome Hepatitis C. It shares the viral and genetic characteristics with a family of flavovuriday (phonetic) viruses. It's a lipid envelope virus.

The genome is a positively sensed, single strand, linear RNA of about 9,000 nucleotides, and it encodes for about 3,000 amino acids.

Near the 5 prime endogenome is the capsid protein and two envelope proteins, E1 and E2; several nonstructural proteins, NS2 through 5, were encoded closer to the 3 prime end of the genome.

The first EIAs developed used small portions of the protein called 5-1-1 from the nonstructural fore region. Later and now more sensitive EIAs employ a broader scope using antibodies directed at an array of antigens. The latest generation of EIAs is the third generation, is directed at antibodies that arise from antigens to the core region, C22, the composite antigen, C200, as well as the nonstructural antigen from the NS5 region.

However, it's important to note that the Hepatitis C antibodies are merely markers of infection and not protective of infection with Hepatitis C. This is in contrast to measuring anti-HAV antibody and anti-Hepatitis B surface antibody, which indicate neutralization of the virus in disease recovery.

This is a nice list that I won't go through in great detail off of a recent issue of seminars in liver disease, and what it will suffice to say here is that the EIA serves using these antigen determinants, uses an important screening tool for the blood supply, and the confirmatory tests are the recombinant aminoblot assay tests. It uses these same epitopes, C100, C33C, C22, and NS5, to confirm or exclude donors and resolve their positive test by EIA, and there are both qualitative and quantitative tests that are available for looking at Hepatitis C virus RNA, nucleic acid used to look more closely at the recombinant immunoblot assay positives and indeterminants, and to assess the responses these individuals might have to antiviral therapy.

The clinical features of hepatitis are reviewed here. It's a disease of insidious onset with an incubation period that varies from two to 26 weeks, with an average of six to seven weeks. The time to seroconversion with the latest generation of antibody tests used to screen the blood supply is about 70 days.

Nucleic acid tests for Hepatitis C RNA will, of course, detect infectious virus much

earlier than this, and we'll show you that in the next couple of slides.

The transmission of Hepatitis C is generally percutaneous and less likely permucosal than is Hepatitis B virus. Few, ten to 25 percent of people, with acute Hepatitis C virus infection develop symptoms. However, importantly 75 percent or more may be asymptomatic.

The larger problem with Hepatitis C, as I mentioned, in contrast to Hepatitises A and B is the high proportion of people who develop chronic infection. About 85 percent of the people infected with Hepatitis C go on to have chronic infection.

Of the persons who have chronic infection with Hepatitis C, ten to 20 percent may develop cirrhosis, and a smaller proportion, perhaps not as high as five percent, but a smaller proportion may go on to develop hepatocellular carcinoma.

What are the signs and symptoms of blood donors who harbor Hepatitis C as a chronic infection? Dr. Shakil at NIH found in a study among 60 former blood donors who had Hepatitis C virus infection, a third of whom had transaminase elevation of more than twice normal, that symptoms,

if they were present, were mild and did not interfere with daily activity.

In a large cohort of NIH donors we have found that their -- that are followed for a natural history of Hepatitis C virus infection -- 70 percent of these have elevations of their ALT or liver transaminases if you follow them over time. Yet of these 60 positive donors in this particular study that went on to have liver biopsy, even though they had more than twice elevated ALTs, only 13 percent of these had severe liver histology when they went to biopsy, and none of those who underwent liver biopsy who had a normal ALT had cirrhosis or severe liver histology.

After over a somewhat longer period of time, and Dr. Alter has looked at post-transfusion Hepatitis C patients, he has found that less than ten percent of Hepatitis C virus infection will sustain liver related mortality and morbidity during the first two decades of infection, and at issue is whether or not these same patients will progress further over the ensuing decades.

This slide illustrates the typical lab course in a patient who is infected with Hepatitis C from transfusion from acute to chronic years

later. Hepatitis C virus RNA is detectable in patient serum between two and three weeks after initial infection, and persists for months, and then years later when tested.

Antibody to Hepatitis C as measured by an early enzyme immunoassay appeared at 12 weeks and has now probably shifted over a little bit to a somewhat earlier time at about ten weeks.

The most recent EIAs, as I say, employ many of the epitopes, a broader array of epitopes across the Hepatitis C genome.

ALT elevation, as shown here by the blue shaded area, peaks here at about week 17 and fluctuates hereafter. It's hard to see, but there's a blue line which indicates normal ALT levels, and you can see even over the years it remains elevated, though fluctuating at somewhat lower levels than after acute infection.

Biopsies that were performed at about 32 weeks and then five years after initial infection indicated chronic active hepatitis and chronic persistent hepatitis.

So in sum, what we can say about this slide is that the Hepatitis C RNA persists. The antibody persists, and ALT fluctuates, but remains

elevated over the course of infection.

The severity of liver disease at this stage of chronic infection is not particularly problematic. However, a small proportion, as I mentioned, of these patients will progress to cirrhosis, and an even smaller proportion perhaps many years later to hepatocellular carcinoma.

In contrast to Hepatitis A, therapy for Hepatitis B and C is available, though it's not highly efficacious. Interferon alpha is used for both. The combination of Interferon and ribavirin for Hepatitis C is somewhat more efficacious than in interferon used alone.

Hepatitis B hyperimmune globulin is useful for perinatal and post exposure prophylaxis and unvaccinated people, though no immune globulin has ever had proven value in Hepatitis C virus infection.

Vaccination against Hepatitis B virus is highly efficacious and commonplace nowadays, though a vaccine for Hepatitis C virus remains illusive and preventing Hepatitis C virus really involves risk factor modification for those who are at risk for acquiring the disease, as well as blood donor screening.

In sum, these last two slides, what I've tried to cover in a very brief period of time is the Hepatitis A, B, and C viruses and their clinical and virologic character. They belong to different virus families, A, B, and C. The onset for each is very different, as is the incubation period, and when one would generalize, you might say one month, two months, and three months for each of the hepatitis viruses, A, B, and C.

The source of the viruses are different. Hepatitis A is an enteric virus while Hepatitis B and C are blood borne viruses primarily.

Hepatitis A does not go into chronic infection, while B and C do, and prophylaxis and prevention of A and B can be achieved with immune globulin preparations and vaccines, while biologics and vaccination schedules and vaccines are not available yet for Hepatitis C.

And thank you. That's all I have for today.

DR. TABOR: Thank you very much, Dr. Cantilera, for that nice overview of the basic virology.

Our next speaker is Dr. Ian Williams, who's a medical epidemiologist at the Centers for

Disease Control and Prevention and is the principal investigator in the sentinel county study. Dr. Williams will be talking to us about the epidemiology of Hepatitis A, B, and C.

After Dr. Williams' talk, we'll have a short period for discussion and then the break.

DR. WILLIAMS: Great. Thank you very much for the invitation today.

What I'm going to try to do in the next 20 minutes or so is cover the epidemiology of Hepatitis A, B, and C. Twenty minutes is not nearly long enough to do that, but I'll do my best, and then at the end, I'm going to try to pull everything together and show you some data that's not widely available from our sentinel county study about people with a history of hepatitis.

The first slide.

Overall in the United States, if you look at acute viral hepatitis, about 50 percent of all acute viral hepatitis is Hepatitis A; about 30 percent or 35 percent is Hepatitis B; about 15 percent is Hepatitis C; and about three percent in non-Hepatitis A. Hepatitis D and E are rarely seen in the United States, and so about three percent is we're not quite sure yet, but there are other

agents out there yet to be decided.

So in terms of the epidemiology of Hepatitis A, as we heard in the previous presentation, Hepatitis A is found in the highest concentration in stools, found in moderate concentrations in serum, found in somewhat lower concentrations in saliva, and typically not found in urine and semen and less blood contaminant.

Since it's found in highest titres in the feces, it's typically spread through close personal contact through a fecal oral route. This includes such settings as day care centers, household contact with infected cases, or through sexual contact. Outbreaks also occur through contaminated food or water, such as infected food handlers who have less than adequate hygiene, as well as through shellfish, which may come from fecally contaminated waters.

Blood exposure has also been reported in the literature, although it is somewhat rare. So Hepatitis A virus transmission can incur through injection drug use, and has rarely been reported through transfusion, although there's some controversy whether injection blood use is actually occurring through -- transmission actually through

an infected drug sharing equipment or actually through close personal contact, but regardless, you do see it quite frequently among injectors.

So if you look at what are the risk factors for Hepatitis A, where do people get Hepatitis A from, and this is data from our sentinel county study over sort of the early to late 1990s, and the number one risk factor is I don't know what the risk factor is, and that's typically because the incubation period is 30 days or so. So most people have no idea where they got their Hepatitis A from.

The second leading risk factor is contact with a case. You know somebody who has Hepatitis A.

The third leading risk factor is men who have sex with men, followed by day care related, and finally international travel accounts for about five to ten percent.

I did this slide by year to show a couple of things. Typically the proportion of these cases varied from year to year. Hepatitis A is an episodic disease, and this is also data from four or five counties, depending upon which year you look at, and in these counties there have been

no large outbreaks associated with food handlers. So in a typical community the relative proportion of these pieces of the pie vary from year to year, and in some communities you can see a very large proportion of cases associated with food borne outbreaks, although we haven't seen it in our sentinel counties at least in the '90s.

As I mentioned previously, Hepatitis A is episodic. You tend to see tremendous waxing and waning of the number of cases in the United States going back into the '50s, and we've seen a steady decline in the number of new cases.

And this slide is a little old. It ends in '93. In sort of the late '90s, we've seen a somewhat up tick again, with probably in the ball park of about 200,000 new infections occurring last year in the United States.

Age is a very important risk factor in Hepatitis A. Almost all the cases we see typically tend to be in people under 40 years of age, with children five to 14 and 15 to 24 accounting for most of the cases, with somewhat lower rates, although relatively high rates, seen among 25 to 39 year olds. So basically almost all cases of Hepatitis A are seen in people under 40 years of

age.

We do see cases in children under five years of age, but as we heard previously, almost all of these people are symptomatic, and this is actually of reported cases. So this is just symptomatic cases.

We do see cases over 40, although they occur rarely.

This is data that you may not have seen before. This is the prevalence of Hepatitis A or anti-HAV from the National Health and Nutrition Survey. This is a national population based survey that was done between 1988 and 1994 to look at a range of health and nutrition outcomes, and this is a population based sample drawn from people all across the United States and meant to be representative of the U.S. as a whole.

And for this study, they tested in the ball park of about 20,000 people and asked them a series of questions and tested them for Hepatitis A, B, and C, and I'll show you the results from Hepatitis B and C later, which have been a little more widely distributed.

But overall, 30 percent of people in the NHANES III study had antibody Hepatitis A, and when

they looked at different population subgroups, about 70 percent of Mexican Americans had antibody Hepatitis A, about 40 percent of non-Hispanic blacks, and about 25 percent of non-Hispanic whites. So there was a tremendous relationship between antibody Hepatitis A and racial/ethnic group.

And there was also another important feature about Hepatitis A, is the epidemiology of Hepatitis A is changing in the United States. This is the third National Health and Nutrition Survey. In the second National Health and Nutrition Survey, they found a very strong relationship between age and antibody prevalence for Hepatitis A, starting at about ten percent of people six to 11 had antibody to Hepatitis A, which increased up to about 80 or 90 percent by people who were over 70.

In the third National Health and Nutrition Survey they saw the same general trend, although many fewer people, especially those over 30, had antibody to Hepatitis A, although by the time you got to 70, still about 70 percent of people were infection with Hepatitis A.

So it looks like the epidemiology of

Hepatitis A is changing and that there is somewhat of a cohort effect; that as the population -- as we go through time and we continue to go through time, the seroprevalence may be expected to continue to drop, although time will tell when we do the fourth National Health and Nutrition Survey.

So let's talk briefly about Hepatitis B. Hepatitis B is found in highest concentrations in blood serum and wound exudates, found in moderate concentrations in semen and vaginal fluid, saliva, and typically not detectable in urine, feces, sweat, tears, and breast milk.

Therefore, Hepatitis B is spread predominantly through perinatally or parenterally, perinatally, and sexually, and this is reflected in the risk factors.

About half of all acute Hepatitis B cases in the United States are sexually transmitted. About 40 percent are sexually transmitted, and about ten to 15 percent are transmitted in men who have sex with men.

Injection drug use accounts for about 15 percent of cases. Household contact with cases, that accounts for about three percent; health care for about one percent; and about 25 percent of

people don't give good, solid risk factors for Hepatitis B. However, if you examine the characteristics of these people, about four percent of them are drug users, although they don't admit to drug use in the last six months. About eight percent report history of STDs, although they've only had one partner in the last six months. One percent have been in prison, and 11 percent have low socioeconomic status, and it's unclear what this means, but clearly these people are different than the general population, and this is defined as people with less than a high school education.

Our general feeling is that a number of people here are what one of our sentinel county's nurses calls this truth challenge. They probably have a variety of these other risk factors, but just aren't admitting to them upon interview.

So someplace in the ball park of about ten percent or so of acute cases have no known risk factor.

A number of new cases occurring every year in the United States has changed quite dramatically. If you look back in the mid to late 1980s, about 400,000 new infections occurred every year in the United States. Right now we're in the

ball park of about 200,000 new infections. So in the last decade or decade and a half, the number of new infections has basically halved, and a lot of this has been due to a couple of things, but predominantly due to the wide use of vaccine, screening of pregnant women, wide use of vaccine not only among health care workers, but among infants and adolescents.

So Hepatitis B is basically going away in the United States predominantly through the wide use of Hepatitis B vaccine.

Here's more data from the National Health and Nutrition Survey, which shows that roughly about five percent of people have any marker of HBV infection. So this is HBSAG and anti-HBC thrown together. So any marker of past Hepatitis B infection.

And like Hepatitis A, there was a strong relationship between racial/ethnic group and past infection of Hepatitis B. About two percent or two and a half percent of non-Hispanic whites had markers for Hepatitis B. About 12 percent of non-Hispanic blacks had markers, and about four and a half percent of Mexican Americans had markers of Hepatitis B.

And like Hepatitis A, there was a strong relationship between age and prevalence of -- that's wrong. It should be prevalence of anti-HBC.

You can see that certain racial/ethnic groups had, again, a very strong relationship between how many were positive and what racial/ethnic group they're in, as well as age. Asian Pacific Islanders and other groups started at a seroprevalence of between five and ten percent at age six and went up to over 35 to 40 percent by the time they were 70 years of age. And you can see in each group the anti-HBC prevalence increased with age.

Let's briefly talk about Hepatitis C. Like Hepatitis B, Hepatitis C is a blood borne pathogen, and I think people tend to forget that, like HIV, and it shares many of the same features in terms of how it's transmitted. It can be transmitted through blood, blood products, organs and tissues from infected donors. It can be spread easily through illegal drug use, both injection and noninjection; in a hospital setting, through contaminated instruments, equipment and suppose, not only those found in traditional medicine, but in folk medicine, tattooing, body piercing, and

razors, as well as through infected contacts, such as sexual partners, household members, pregnant women, patients and health care workers. So it's a traditional blood borne pathogen, although the epidemiology of Hepatitis C is somewhat different than Hepatitis B.

When you look at the epidemiology of Hepatitis C and risk factors for it, you have to draw a line in the sand about 15 years ago. More than 15 years or so ago, transfusion was the leading risk factor. About 40 percent of all new cases were associated with transfusion. About another 40 percent were associated with illegal drug use. In the ball park around ten percent or so were associate with sexual transmission.

As we heard about earlier with increasing safety and protocols instituted in the blood supply, transfusion associated Hepatitis C has pretty much gone away in the United States, although it still occurs rarely.

And what has happened by taking this major part of the pie out is the other parts of the pie have taken over, and in the ball park of about 60 percent of all new cases of Hepatitis C seen today in the United States are associated with

illegal drug use, predominantly injection drug use, and in the ball park of 15 to 20 percent are associated with sexual transmission.

If we look a little more closely at the data over the last -- in the '90s, what we find is about 40 percent of people with acute Hepatitis C admit to injecting drugs in the last six months. About 16 percent of people admit to having sex with somebody or are known to have sex with somebody who has Hepatitis C. That's about two thirds of these people, and about one third of them are having more than two sex partners in the last six months. So in the ball park of around 15 to 20 percent of cases are sexually transmitted.

About three percent of people are living in the household with somebody with Hepatitis C. About four percent of people report an occupational risk contact with blood, and about four percent is transfusion associated, although it should be noted that since 1995 we haven't had a transfusion associated case in the five sentinel counties. We still think they occur. It's just so rare we haven't seen them.

About 30 percent of people report no specific risk factor, like we saw with Hepatitis B,

although again, if you look at these people more closely, about 14 percent of these people report drug related activity. Ten percent of them report ever injecting drugs, but just not in the last six months. Four percent of them reported starting drugs, and one percent report contact with injecting drug use.

Two percent have been in prison, and four percent have a history of an STD.

Our general feeling is that, again, a number of these people are truth challenged, as our nurse says, and a lot of these belong in some of these other categories. They just won't admit to it on interview.

The bottom line here is that about ten percent of people have no identified risk factor, and that injection drug use accounts for almost all of the new cases of Hepatitis C we're currently seeing in the United States.

And to bring this message home a little clearer, this is data from a study done in Baltimore where they basically took a group of injectors and asked them how long they had been injecting, and then tested them for HIV, Hepatitis B and Hepatitis C, and what they found is HIV came

in number three in terms of blood borne pathogens. Between 15 and 20 percent of people were infected on baseline, and this slowly but surely went up to about 20 to 25 percent.

Hepatitis B virus infection came in second. Again, this is any marker of Hepatitis B. In the ball park of about 40 percent of the people were on baseline, and this slowly but surely went up to about 70 percent or so.

What was a little shocking to these investigators and has been replicated in lots of other studies is that about half of the people were already infected with Hepatitis C within the first four months of the time they started injecting, and this very rapidly went up to 80 to 90 percent.

So the bottom line is most injectors are infected within the first six months or a year of the time that they've been injecting, and this has been repeated in studies all across the United States. Where people have injected for more than a year, roughly 80 to 90 percent of them are infected with Hepatitis C.

I thought I would talk about sexual transmission, Hepatitis C, since this is probably the question I get asked the most. Well, how can

15 or 20 percent of acute Hepatitis C be sexually transmitted? We just don't see that in partner studies. I'm a little confused about it.

So what I thought I'd do is sort of lay out the data and show some of the controversy. Basically if you look in case control studies of acute disease, Hepatitis C seems to act like a traditional STD. Exposure to infected partner and multiple partners, all have been found to be independent predictors of acquiring acute Hepatitis C.

And if you look among people with high risk sex practices, such as people in STD clinics, basically infection has been related to increasing number of partners, nonuse of condoms, other STDs, and sex with trauma. So, again, this tends to look like a traditional STD.

However, when you look a little more closely, men who have sex with men are typically at no higher risk than heterosexuals in this setting. So it sort of doesn't look like an STD because we know men who have sex with men are much higher risk of both Hepatitis B and HIV.

And when you compare the prevalence of Hepatitis C against Hepatitis B and HIV, the

prevalence tends to be much, much lower. So it kind of looks like an STD, but a nontraditional STD, and this was sort of borne out in partner studies where the average prevalence among partners is about one and a half percent, which is about what you see in the general population.

However, in some of these studies, male to female transmission may be more efficient. So it sort of looks like an STD, doesn't look like an STD. So what's the bottom line?

Well, sexual transmission of Hepatitis C does seem to occur, but the efficiency seems to be low, and it seems to be exceedingly rare among long term steady sex partners. How rare is not exactly known. Some studies are underway to try to put a better number on than just rare.

However, we do know it accounts for 15 to 20 percent of acute and chronic infections, and there are a large reservoir of people out there with multiple opportunities of exposure. Roughly 2.7 million people in the United States are chronically infected with Hepatitis C, and we really don't know factors to facilitate the transmission of Hepatitis C, such as viral titres and other STDs, especially ulcer STDs, which may

actually take this risk from low and make it somewhat higher.

So a lot more work needs to be done to define or to learn about sexual transmission of Hepatitis C.

So with that all said about the risk factors, how many new cases occur every year in the United States? Well, if you look back into the mid to late 1980s, there were in the ball park of about 200,000 new cases occurring every year in the United States. Today we're seeing in the ball park of about 40,000 new cases, and a lot of this decline has occurred among transfusion recipients, as we talked about previously or as you heard about previously, although there's been a tremendous decline among injecting drug users in the late '90s as well.

It's a little unclear why the number of new infections has been dropping quite dramatically, but it is a fact that it's declined from about 200,000 new cases to about 40,000 new cases every year in the United States.

So how many people are infected with Hepatitis C in the United States? Well, this data has been widely published and circulated around.

About 1.8 percent of the U.S. population has been infected with Hepatitis C, and this translates into four million Americans. It's about 3.9 million people, and again, there's a strong relationship between racial/ethnic group and previous NAHCD positivity. About three percent of non-Hispanic blacks have been infected with Hepatitis C, about two percent of Mexican Americans, and about one and a half percent of non-Hispanic whites.

And again, there's a quite strong relationship between age and prevalence with Hepatitis C. However, this looks a little bit different than Hepatitis A and Hepatitis B in that there's a very characteristic hump that's occurring among middle age groups, and actually I've just drawn some arbitrary lines on here to try to get a handle for sort of the magnitude of some of these humps that have occurred.

If you look among people that are 30 to 50 years of age, an average prevalence of about three and a half percent occurs among this age group, and a somewhat lower prevalence of about one percent occurs among those older than 50. This sort of suggests that Hepatitis C is a relatively newly acquired infection in the United States.

It's only been widespread in the last 30 to 40 years, and that as these people age, they'll start to suffer the chronic consequences with Hepatitis C, and over the next 20 or 30 years the number of people suffering severe liver disease caused by Hepatitis C should go up substantially, maybe even as much as triple.

So let's try to put this all in context and sort of compare and contrast Hepatitis A, B, and C. Well, the first important take-home message is that the prevalence of Hepatitis B and C varies very dramatically depending on which risk groups you look at. Again, as we've heard about, the prevalence of Hepatitis B, any markers, about five percent in the general population and about 1.8 percent for Hepatitis C.

However, if you look among men who had sex with men, prevalence of Hepatitis B is in the ball park of 20 to 40 percent. It's only around four percent for Hepatitis C.

If you look among infected sex partners, about 40 percent of infected sex partners have Hepatitis B, where only about one and a half percent have Hepatitis C, and the sexual transmissions also reflect in the number of

lifetime sex partners, and this is from the National Health and Nutrition Survey. And you can see a strong relationship between prevalence of Hepatitis B and prevalence of Hepatitis C with increasing number of lifetime sex partners.

And again, injection drug use is probably the most important risk factor for Hepatitis C. Fifty to 90 percent of people who have injected drugs are infected with Hepatitis C, but so are 60 to 80 percent of people who injected drugs infected with Hepatitis C.

And since we're talking about blood donors, to put this all in context, in the ball park of about .2 percent of first time blood donors are infected with Hepatitis B, and this is HBSAG, not any marker of Hepatitis B, whereas about half of a percent are infected with Hepatitis C upon first time donation.

And if you look at repeat donors, and again, this is incidence, not prevalence, the incidence tends to be very, very low, in the ball park of .0035 percent, and this is sort of an unusual way to present incidence for those of you not used to seeing this data. This actually translates into about three and a half per 100,000

person-years of follow-up, and this data is actually from the Red study, and there have been some recent publications that suggest that the incidence of Hepatitis B may actually be a little bit higher than this if the mathematical model is used.

But the point is that the incidence among repeat blood donors still tends to be very, very low.

It's also important to put Hepatitis A, B, and C sort of on the same axis. On all the previous slides, they were all different axes over here. You can see quite clearly that Hepatitis A is quite prevalent in the U.S. population. Overall 30 percent of people are infected with Hepatitis A, and even if you look at people under 20 years of age, roughly ten percent of people are infected with Hepatitis A, and you can see the relative proportion, that very, very few people under 20 are infected with Hepatitis B or C, and predominantly all cases of acute hepatitis occurring under 20 years of age is attributable to Hepatitis A.

And this is pretty much true among any case of hepatitis that occurs in the United States in terms of its relative proportion to Hepatitis A,

B, or C. It's almost all Hepatitis A.

An important factor to remember, on the previous slide I showed you seroprevalence, that is, markers of people with -- seroprevalence doesn't account for the number of actual acute cases that are occurring.

You'll notice that as we heard in the previous talk that almost all children tend to be asymptomatic. So this doesn't account for asymptomatic cases, but roughly half of people with Hepatitis A, children are symptomatic again, but very few Hepatitis B cases are symptomatic, and it's a little unclear whether children are symptomatic with Hepatitis C at all.

So the bottom line is most cases that we're seeing in terms of actual acute cases are asymptomatic.

Now, in the last two slides, I'm going to show you some data from the sentinel counties. What I actually did is took people with acute Hepatitis A and actually looked at how many of them reported a history of viral hepatitis, and then stratified by age, and the reason I picked cases of Hepatitis A is that cases of Hepatitis B and C are quite different than the general population.

People with Hepatitis A seems to be relatively representative of the community at large.

And what you find is basically no one under 20 years of age reports a history of hepatitis. Basically this is one person out of about 600. About five percent of people 20 to 30 years of age report a history of hepatitis, and about eight percent of people older than 40 years of age report a history of hepatitis.

However, if you actually test these people and say how many had serologic markers for Hepatitis B or C, you basically find that about five percent had markers of Hepatitis B or C under 20. In the ball park of about 20 percent or 25 percent had markers who have post-B and C, 20 to 30. In the ball park of about 40 percent had markers of Hepatitis B or C over 40.

So the point is that most people don't know they had a history of hepatitis. However, if you look at people who did report a history of hepatitis and say how accurate were they, basically you find that the people do a pretty good job. Since only one person reported a history of hepatitis under 20, this data is not too meaningful, but if you look at people -- the 60

people 20 to 30 years, basically most people did a pretty good job of knowing whether they had a prior history, and it got a little better at those over 40.

So what's the bottom line? What conclusions can I make? The first is the prevalence of serologic markers for Hepatitis A, B, and C vary quite dramatically by risk factor or by risk group, as well as age. At least among acute Hepatitis A cases in sentinel counties, very few people report history of hepatitis, but this increases with increasing age.

Many people with serologic markers of Hepatitis B and C do not report a history of hepatitis. So a lot of people don't know they've been infected. However, for people who do report a history, most of them know whether they had Hepatitis B or C.

Thank you very much.

DR. TABOR: Thank you very much.

I think we're running just a little late, and maybe we should take the break now and return at 10:25, and we'll postpone discussion until just before lunch and maybe run into the lunch hour if we have to.

So until 10:25.

(Whereupon, the foregoing matter went off the record at 10:05 a.m. and went back on the record at 10:31 a.m.)

DR. TABOR: I know a lot of interest was expressed in the last two slides from the NHANES III study concerning history of hepatitis, and we'll come back to those just before lunch hopefully.

Are there any other questions? Dr. Bianco?

PARTICIPANT: I actually asked this question of Dr. (inaudible) outside, but I think that the issue for us is not how many people that have an acute history of hepatitis have markers, but our question is if you take the general population and you look at the history, and now you take at least our donor population and we test that population, what is the prevalence of markers? I don't think that they have that.

That would be determining the sensitivity of the question and specificity.

DR. TABOR: Yes, Steve.

PARTICIPANT: Yes, I had another question for Dr. Williams. On the epidemiology

slides --

DR. TABOR: Excuse me just a minute. Is there any way you can turn on the microphones from back there? Okay, I think.

PARTICIPANT: I don't know if that's any better.

DR. TABOR: Yeah, that's better.

PARTICIPANT: On the epidemiology slides for Hep. C, you had something about spread from household contacts, as well as -- and I don't know if they were on the slides, but I'm interested in other percutaneous exposures, like body piercing, tattooing, and also interested in cocaine snorting, the kinds of things that we defer donors for and which CDC often talks about, but we don't actually -- I guess my question is: what is the data that supports household transmission or is this just sort of by exclusion?

DR. WILLIAMS: I think there is very little data. I think it's important to differentiate in the U.S. at least between what does transmit Hepatitis C and what can transmit Hepatitis C. What does is predominantly drugs and sex.

Any sort of exposure to blood could

potentially transmit Hepatitis C. At least in our sentinel county study we do not see Hepatitis C transmitted through body piercing, tattooing, ear piercing, internasal cocaine use, crack use. We asked questions about all of those things. We don't see acute cases who report those risk factors who don't also report injection as well.

Does it mean that you can't transmit Hepatitis C that way? The answer is, no, you probably can. It just probably happens probably very, very infrequently.

And one of the other problems is a lot of these risk factors that you're talking about, intravenous cocaine use, are very socially stigmatized. So a number of people say, "Yeah, I used to snort a little coke, but I never ever injected drugs," but as you get to know these patients, we basically find almost all of the patients are injectors once we interview them and interview them extensively.

PARTICIPANT: Yeah, I think especially the body piercing question is an important one for blood banks because especially if we want to attract younger donors. You know, those behaviors are so frequent now, and I think as will come out

in the discussion period, if you do defer somebody for 12 months, you are really under a misguided concept if you think that person is going to come back because the few studies that have been done suggest that once people get deferred, they usually have had a negative enough experience that even if they're eligible in the future they don't come back in.

So I think it's something that hopefully we can talk about a little bit more in the panel discussion

DR. TABOR: I had a discussion with Miriam Alter a few days ago about that issue, and she maintained, and I think I have to add the proviso that this is third hand, but she maintained that body piercing is now being done by a group in a different subculture than it was some years ago, and that as you said, it's often the young people, many of whom are not in the drug culture, and that it appears to be a very low risk.

DR. WILLIAMS: Yeah, I think the comment I'd make is there's body piercing and body piercing and tattooing and tattooing. I think in some settings there is definitely transmission. For example, prisons, where there may be reuse of

needles, reuse of ink, one towel to clean, and in that setting it's almost like sharing injection drug use equipment.

But studies need to be done to sort of figure out is all body piercing the same. Are there certain settings where the risk is actually a lot higher?

DR. TABOR: Okay. I think we're ready to begin. The next speaker is Dr. Ray Koff, who's an extremely noted hepatologist and has agreed to take on an extremely difficult subject.

Between the FDA regulation concerning the exclusion of donors with a history of hepatitis and the wording of the American Association of Blood Banks' questionnaire over the past several decades regarding the same issue, a different wording has appeared, and it's certainly open to different interpretation.

And we've asked Dr. Koff to discuss clinical aspects of different definitions of hepatitis that are used in these blood screening questions because we could be talking here about the FDA regulation which says a history of hepatitis, which we've interpreted to mean a history of clinical hepatitis, and somebody else

might be talking about a questionnaire that says a history of jaundice.

Dr. Koff is professor of medicine at the University of Massachusetts Medical School in Worcester.

Dr. Koff.

DR. KOFF: Thank you, Ed.

I'm just a clinician, and I don't really know very much about blood banking. I thought I was invited here because I happen to be a frequent blood donor, and I brought with me my donor registration card from my hospital, and Question No. 6 -- and by the way, there are 34 questions that I'm asked every eight weeks -- and Question No. 6 says, "Have you ever had yellow jaundice, liver disease, hepatitis, or a positive test for hepatitis?"

And Question No. 15 is, "In the past 12 months have you ever had close contact with a person with hepatitis or jaundice or have you had HBIG injection?"

Well, I always lie because I only see patients with liver disease and many patients with jaundice and hepatitis. So I say, no, I don't have any contact. At least the contact I have I think

is -- I'm very fastidious so it shouldn't be a problem.

But I guess what I'm trying to direct my comments to are the questions listed here. What does a history of hepatitis mean? Is hepatitis necessarily always viral? Are there ways clinically of distinguishing between one and another?

Let's see.

DR. TABOR: The screen has changed due to your adjustments. Can you give us some advice? We'll need a technician down here. The screen has changed.

DR. KOFF: Or can I say, "Next slide"?

Okay. Great. Well, the question I want to approach is how do patients learn that they, in fact, have hepatitis, and some of this will be related to clearly symptoms of acute disease, what we've heard before, the clinical setting of hepatitis with nausea, vomiting, anorexia and/or jaundice.

Some will give a history of having learned they have hepatitis because they have symptoms of chronic liver disease, such as fatigue or more advanced disease.

We see a number of individuals who find out they have hepatitis as a consequence of routine multiphasic screening. They change their health insurance. They need a new primary care physician, and until fairly recently it was possible to do multiphasic screening. Not anymore because if you do multiphasic screening and you don't find anything, someone else is going to have to pay for those tests. So we don't see much of that.

But insurance exams, there is now fairly conventional testing for ALT, AST on insurance, life insurance examinations, and of course, we continue to get some patients out of blood banks because of an elevated ALT and other patients who present because of complications of liver disease and have been told.

Simply to remind you that all jaundice is not hepatitis, here is a clear scleroictoris away from the cornea, seen best in the fornices. Just to remind you, it can be fairly subtle. It is not a specific or a sensitive manifestation of hepatitis. As we'll go over, it can be seen in a variety of liver disease of biliary tract disease or, in fact, with hemolysis.

Jaundice is generally not recognized

until the serum bilirubin is in excess of two and a half milligrams per deciliter, and even then it takes a clinician who's reasonably aware and has an index of suspicion to find it.

As you've already heard, it is present in only a variable proportion of patients with acute viral hepatitis, and that is related to a number of factors, the type of hepatitis they have, and as we will hear if we haven't heard already, can be age related.

So that adults with Hepatitis A commonly are jaundiced, whereas children infrequently will have jaundice as a manifestation.

Roughly 70 percent of the adults will have jaundice. The available information on Hepatitis B suggests anywhere from a third to 50 percent, and again, based on limited studies, largely coming out of the sentinel county experience, some 20 percent to perhaps a third of patients with acute Hepatitis C will, in fact, have a symptomatic disease with jaundice, therefore, meaning that the rest of those individuals who are infected will not be recognized because they will not have either jaundice or other clinical manifestations with are sufficiently specific to

lead someone to a diagnosis of acute hepatitis.

So jaundice is, in general, uncommon with kids with hepatitis, and since most of the hepatitis seen in children is going to be Hepatitis A rather than acute B or C, jaundice is not particularly useful, and therefore, the 11 year rule of thumb that has been mentioned here may be appropriate.

In adults, on the other hand, the frequency of jaundice is different, and dramatic elevations of the serum bilirubin are clearly more common than in children.

Asymptomatic hepatitis does, of course, get recognized, and individuals will be told that, in fact, they have suffered or had a bout with hepatitis, and that can be a consequence of, again, the incidental detection of a laboratory abnormality on multiphasic screening or during the course of investigation for an elevated or abnormal liver test by doing a panel of hepatitis serologies and identifying someone as having evidence of acute infection or, less commonly, when we monitor people, household contacts or other individuals who have been exposed by doing either liver chemistry monitoring or serologic monitoring.

And, again, such individuals, even though they may not have any clinically apparent disease, will be told that they've had hepatitis, and they carry that diagnosis with them to the blood bank, as well as elsewhere.

But all jaundice is not hepatitis, and I wanted to just quickly go over some of the other things that will pop up if you ask a patient have you ever had jaundice, and of course, many of these are things that are associated with clinical illness, but yet may not come to clinical awareness for some time.

Obviously hemolysis, acute hemolysis, as well as those disorders that are associated with chronic hemolysis, sickle cell anemia, thalacemia, pernicious anemia, in effective erythropoiesis as a consequence of Vitamin B-12 deficiency; individuals who have large hematomas following surgery or motor vehicle accidents may, in fact, develop transient jaundice, and although stored blood is not used very much anymore, I don't think, at least in the past the transfusion of large quantities of stored blood, blood stored more than 21 days, for example, was associated with the development of jaundice as a consequence of the breakdown of some of those

older cells.

Then there are the uptake and conjugation defects. The most common one which I'll say a little bit more about, Gilbert's syndrome. Physiologic jaundice, we've already touched upon that. Neonatal jaundice, infants who have either immaturity of their bilirubin glucoronal transferase. The rare Crigler-Najjar syndrome in which there is, again, deficiency of or complete absence of the enzyme bilirubin glucoronal transferase.

There are a number of drugs that can induce unconjugated hyperbilirubinemia, the most common of which is probably rifampin, and then an unusual set of disorders, such as heart failure, mild unconjugated hyperbilirubinemia can be seen.

The most common disorder, of course, is Gilbert's syndrome, and in these individuals, on average, the serum bilirubin is less than five. It is exceedingly common. Every year I see at least one new case among our house officers or among the medical students, and the reported prevalence of this has varied between one and seven percent. When you really look for it, the seven percent figure comes from an old study done at the College

of Physicians and Surgeons when the medical student class was analyzed by Arthur Coinberg (phonetic), who subsequently won a Nobel Prize for other work, not for that.

Well know that intercurrent illness and reduced caloric intake is associated with a rise in serum bilirubin in individuals with Gilbert's, but it's not a liver disease, and these individuals have no evidence of any defect other than Gilbert's. Many of them have actually gone into liver disease and become hepatologists and have had long and wonderful lives.

There are a couple of other disorders, hereditary, that can be confused because they do present as jaundice. They are rarities. Dubin-Johnson syndrome and Rotor's syndrome. I haven't seen a Dubin-Johnson in 25 years. Rotor's, to the best of my knowledge, there are only two or three families in the world with this, and you're just very unlikely to hit one of these individuals.

Again, they have a defect in organic anion excretion and no serious liver disease.

And then, of course, there's the large variety of what a clinician deals with, the interhepatic disorders that can be associated with

jaundice, not only viral hepatitis, but alcohol induced liver disease, drug induced liver disease, and autoimmune liver disease, a disease largely of women but of variable age and of variable presentation.

There are other disorders that someone like myself thinks of when I'm dealing with an individual who has jaundice. The emerging liver disease of the millennium will be nonalcoholic steatohepatitis, a disease originally identified following the jejunoileal bypass, but now recognized with increasing frequency in diabetics, in obese individuals. Etiology is not really very well understood. Treatment is at the moment uncertain.

There are other disorders, benign postoperative cholestasis, Gramm-negative sepsis, patients with hypernephroma who experience hepatic dysfunction, rarely in lymphoma, and then the list of disorders goes on and on.

But these individuals are not likely to be blood donors. These are individuals who have clinical illness who are likely to exclude themselves. They're not likely to be motivated to be blood donors, and will probably not pass initial

screening by any reasonable blood bank.

Oops. I didn't mean to do that.

And then the extrahepatic disorders that may be associated with jaundice. The simple one, such as gall stone obstruction, acute illness, pancreatitis, malignancy, and then disease of the bile ducts including strictures, sclerosing cholangitis, and of course, sclerosing chorangiocarcinoma.

And, again, these are in a different set of patients and are unlikely that these individuals will get to the blood bank, although someone who had a cholecystectomy for jaundice as a 25 year old could show up at age 50 and only give a history of jaundice, and unless one asked and actually looked at the abdomen to find the little signs of laproscopic surgery, one might exclude such an individual unless a full history was gotten.

Even in pregnancy jaundice raises a whole spectrum of illnesses. Hepatitis is the number one cause of jaundice during the course of pregnancy. On the other hand, gall stones, hyperemesis gravidarum, interhepatic cholestasis rarely occurs during the first trimester. I've broken these down by trimester.

Second trimester, it's still viral hepatitis is the most common cause of jaundice, gall stones the second most common. Then we get into the preeclampsia, clampsia, and a few more cases of interhepatic cholestasis.

And then in the third trimester, interhepatic cholestasis goes up. We have the HELLP syndrome or hemolysis, abnormal liver tests, and low platelets; rarely acute fatty liver of pregnancy and hepatic rupture as causes of jaundice during pregnancy.

And then just to end, again, we can do this by age and infants and neonates. It's going to be physiologic jaundice, the major cause; some congenital infections; some metabolic disorders, although fairly rare. By the time you're an adolescent, it's largely Gilbert's and hepatitis, and as we move through the young adult stage, hepatitis becomes an even more important problem, particularly with Hepatitis B and C, and then in the elderly, it's a new set of problems related to malignancy.

So I think the point I wanted to make is that a history of yellow jaundice has to be taken with -- I don't think can be used by itself. I

think more questions have to be asked about that.

I think asking about liver disease is interesting, but, again, I think one needs more details, and I'm not sure that a blood bank or blood bank technician has either the time or the expertise to go through a differential diagnosis of what that likely liver disease is, and since patients do forget and don't remember the details of what they were told, I wonder how much value that has.

As I've already heard, you are already discriminating between a positive test for hepatitis and a history of hepatitis, and that, in fact, may be all you need to do.

Thank you.

DR. TABOR: Thank you very much.

I think that really addressed the question perfectly, and we're going to have to come to grips with that in our discussion this afternoon.

I also appreciate your bringing your blood donor card because it illustrated very clearly how broad and nonspecific the questions are.

The next speaker is Dr. John Ticehurst.

Dr. Ticehurst is a medical officer in FDA's Center for Devices and Radiological Health. He works very closely with the regulation of some of the test kits for hepatitis that are not used for blood, and he is also very active as an assistant professor at Johns Hopkins University School of Medicine.

Dr. Ticehurst has a distinguished prior career in research in Hepatitis A virus, and he's going to speak to us today on the significance of a history of having had either Hepatitis A or Hepatitis E.

DR. TICEHURST: Good morning, everybody. Thank you.

Thank you, Ed, for that nice introduction and, Robin, for inviting me.

At the break I saw -- Blaine Hollinger walked up to me and said, "John, you look awfully tired. You look like you have the weight of the world on your shoulders," and I was up later than I wanted to be last night, and if I could have some help getting this projection on, that would help, too.

But I've also -- maybe I don't know whether this is appropriate or not, but I sort of put myself out on a limb here, and maybe that's why

I feel I have the weight of the world on my shoulders. That is not my Stingray up there.

And could we -- one of the technical folks, how do we get this computer to project, please? Isn't modern technology fun?

In any case, the title that I have on my slides -- and there are about 50 copies of the slides I'm projecting out -- I think they're out on the back table, and we can get more. I particularly wanted that because I have a rather complicated table at the end for the discussion later on.

And while our technical colleague is working here -- you don't have to leave, Blaine. Pardon? Okay. While we're getting the slides going, I'll just make some introductory comments.

The title that's listed in the agenda is slightly different than the one I use. "Significance of a history of Hepatitis A or E." I perhaps didn't pay attention to that, but what I came up with, the suitability of donors with a history of Hepatitis A or E, and basically I concluded very quickly that that history is significant because neither virus causes chronic infection or is frequently associated with

parenteral transition -- I'm sorry -- parenteral transmission. So why not use them as donors?

What I'm doing now is speaking through what's on not that stuff, but what's on the first slide. It's the second slide on the handout.

The concern I came up with in thinking about this was the accuracy of the -- here we are now -- the accuracy of the correlation. Thanks an awful lot. Sorry to make your morning miserable. The accuracy of the correlation between serologic or historical evidence of an infection of HAV or HEV and an episode of hepatitis.

In other words, how closely linked are these? That is, put it the other way: could that episode really have been due to an agent like HBV or HCV that we're worried about?

And in thinking about this further, I have sort of assumed that HAV or HEV don't act as surrogates for things like HPV or HCV or something unknown. Keeping in mind that the sort of exemption that's in place now, the idea of asking people if they have a history of hepatitis, that's being used as a surrogate marker.

Well, I don't have my donor card with me, but I have a case. I was talking about this

with colleagues at Hopkins yesterday, and one of my colleagues up there said, "Hey, that's just like me."

He's about 33. His parents were in the Foreign Service, and he grew up worldwide. About 1970 when he was around four, he was living in Mexico City, and they bought some Italian ice on the street, and he got hepatitis. Maybe it should have been called Mexican ice.

Recently he's been tested. He works in a laboratory that does research on Hepatitis C virus, and he's become their control, his sera at any rate. He's positive for total anti-HAV. He's been vaccinated, and he's negative for other markers.

Every time he goes to donate blood he's deferred. He doesn't get asked the 11 year old question.

Okay. So here's where I start going out on the limb. I'm going to present an algorithm that's sort of a straw position that's based on some additional questions to the 40 or so that Dr. Koff has asked.

The possibility, if it exists, of written documentation of the historical laboratory

data where the most important information would be positive results for IgM or total anti-HAV. These are U.S. assays that have been approved for use in the United States.

Thirdly, if necessary and when appropriate, current -- that means at the time of the donation -- testing for total anti-HAV by using a moderately sensitive assay, and that terminology will become clear in a minute or two.

What I'd like to do before I go into the algorithm question is look at some of the pieces of evidence, and looking at what I've called in quotes a positive predictive value for donor suitability, this is not the same as a positive predictive value for diagnostic purposes, and in part, it represents educated or ignorant guesses on my part.

First, I'm doing this fancy-wise here so you can take your own guess and see if you agree with me. The first bullet here refers to hepatitis occurring in less than an 11 year old, which is the current CBER policy, and I put a question mark, moderate, after that.

Again, having that history is moderately predictive of a correlation between an episode of hepatitis and having that hepatitis being Hepatitis

A. Okay? That's the correlation.

One thing that hasn't been discussed today, and I think it might be relevant but I'm not sure, is people who didn't grow up in nonendemic areas. So, in other words, did you not live during childhood, particularly the first 11 years of your life, in those areas that are recognized as nonendemic and you had hepatitis greater than 11 years old? I think at that point that's a very low predictive value for that hepatitis being Hepatitis A.

And then lastly, if you had your so-called Hepatitis A during an outbreak in these nonendemic areas that include the U.S., anybody of any age, there I would think that maybe that predictive value is moderate.

Okay. Now, let's look at the laboratory data with the same kind of consideration. I think everybody would pretty clearly accept that if you have positive results at the time of the illness from both IgM and total anti-HAV, that that predictive value would be very, very high. There may be a number of cases where there's only a positive result for an anti-HAV only, and there I think it's still very high.

It's interesting. I was going into the background of some of this. I went back to a chapter that Blaine Hollinger and I wrote, in which Blaine did the writing on that part of the chapter where he said in a diagnostic situation that the IgM, anti-HAV positive result should always be supported by a total anti-HAV positive result, in other words, having another piece of positive information to support its specificity.

And just a comment here on the footnotes. In terms of these U.S. approved assays, the first assay that was approved for IgM, anti-HAV was the Abbott RIA in 1982, and then in terms of total anti-HAV during illness where that's the only marker, I think I sort of concluded that that has a high positive predictive value for the setting we're talking about.

If the testing is done now with a moderate sensitivity assay, the first one of which was Abbott's HAVAB (phonetic), approved in 1979, and over the past year, couple of years, we at CDRH have been getting inquiries and submissions for assays that are at a higher level of sensitivity. Many of these assays uses a calibrator or as a control reagents that are referred back to the WHO

reference Ig standard, and they attempt to have an analytical sensitivity cutoff of ten to 20 milli-international units per mL based on that WHO standard.

That's really not well stated for the moderate sensitivity assays of which the HAVAB and its EIA descendants, for example, but they're probably in the 50 to 100 milli-international units per mL range, and in reviewing the data that's in the package insert for this first one approved, the DSR one, there are a lot more positive results in the sort of analytical specificity data compared with what they refer to as a comparator of a moderate sensitivity.

So what about the Ig? I think since the key piece of information here is the IgM, anti-HAV assay, what about its positive predictive value in general?

These assays are highly specific from a microbiologic point of view, which may be obvious to people who work with HAV because this is a very unique organism virologically, but the other thing to consider is the matrix in which this -- in which the control -- I'm sorry -- the reagent antigens are in. Initially in the HAVAB-M assay it was HAV

not purified from the livers of Tameran marmosets and in the Organ on Technica (phonetic) assay originally proved it was feces.

Subsequently these have changed to cell culture, and I'm pretty sure they're still not purified, but in any case, those don't seem to present a problem.

The original studies of which -- and in the handout I neglected to give the full reference here -- Decker and his colleagues at Abbott did establish high analytical and, within the limits of their studies, clinical specificity for the assays.

Subsequent reports, and I searched only from like up to about 1985 here, raised some questions about the clinical specificity. In a number of these studies, of which the examples are listed here, persistent reactivity, not necessarily persistent IgM anti-HAV, but persistent reactivity is detected up to 420 days after the acute phase, and in a couple of studies it suggested that some of that reactivity at least is due to a rheumatoid factor, not an IgM rheumatoid factor, but a rheumatoid factor that may be directed against IgA and the presence of IgA anti-HAV.

Okay. Now, I go into this sort of

algorithm. Here are the questions that I'll throw out as possible questions.

This is one that's already being used. Were you less than 11 years old when you had your Hepatitis A?

Secondly, did you live entirely within these so-called nonendemic areas during the first 11 years of your life?

And, thirdly, did you have Hep. A during an outbreak in U.S., Australia, Japan, or Northern Europe?

And a fourth question, which I think is probably relevant today if we're going to ask these: have you been vaccinated against Hep. A? Because if the answer to that is yes, there's no point in testing for total HAV at the time of the donation. It will confound the analysis, and it will possibly present problems if it's negative for reporting back to the donor.

Here now is where I've put some of this data together, where I've taken some interpretations using the different types of documentation I've just gone through, several sample patterns. There are obviously a zillion different permutations that could come up here, and

let me just go through a few of these.

In my thinking, if you have the historical data based on approved methods for both total and IgM anti-HAV, I don't really care what the rest of the information is. That's probably an acceptable donor.

If, on the other hand -- bear with me just a second, please, here -- if you don't have data from the total anti-HAV during the disease and the current testing is negative, the question is: would you accept that person? Would you defer them with opportunity for reentry later?

Another example here, this is basically just an extension of the current CBER practice where there are no data, and the hepatitis has occurred in someone who's grown up in the U.S. or a nonendemic area and had their hepatitis less than 11 years old. The only new information is a positive total anti-HAV.

I put a question mark there just to raise the possibility of the specificity or the predictive value of that information.

A couple of other instances where the donor could be accepted by my way of thinking would be someone who with no historical data, positive

recurrent testing for total HAV; it doesn't matter when they had their hepatitis, but they had their hepatitis in an outbreak in a nonendemic area, thinking that such hepatitis would almost certainly be due to Hepatitis A.

On the other hand, if somebody grew up outside the U.S., the outbreak would very likely be due to Hepatitis E.

Another example here of someone who grew up outside the U.S., but had their hepatitis less than 11 years old, similar to this situation. I would consider them acceptable as a donor. The distinction here is that if -- my thinking is that if you grew up in an endemic area for Hep. A and you had what you're calling Hep. A when you're greater than 11 years old, that that's unreliable information since the vast, vast majority of them would have been infected by the time they're five years old.

Okay, and then in terms of a couple of examples of deferrals, most of the sort of scenarios I played out ended up in deferral. A couple of examples here, both of these with no historical data.

The positive anti-H -- the total anti-

HAV from currently testing is negative, but there's absolutely no information to -- I'm sorry. This would be in somebody who had a history of hepatitis greater than 11 years old.

And then another situation where the person has been vaccinated. They had their hepatitis greater than 11 years old. This is actually pretty similar to the situation now without doing the testing, but there's no point in the testing. Current testing for total HAV would be not helpful there.

Hopefully that's clear, but you've got it in front of you. You can discuss it later.

Another point I wanted to bring up with this, something that swayed my thinking in all of this is that these folks are all going to be tested for markers for HBV, HCV, and HIV, and particularly with regard to HBV and HCV I think it's a valid assumption that negative results for this issue of donor suitability in these settings has very high negative predictive value, and that's certainly the way they're used now.

Okay. So concluding here for Hep. A, certain types of documentation, for example, the IgM anti-HAV positive can lead to donor acceptance,

but as I went through all of this and struggled through making that table and hopefully you had some of the same angst, I came to the similar sort of conclusion that Dr. Koff did, a little different direction. Is collecting and analyzing such documentation worth the trouble, or perhaps is there a simpler algorithm?

I was talking with Ian Williams during the break, and he indicated one of the gists of his last slides he showed was that if people remember a history of hepatitis, it's almost certainly due to Hep. A. So maybe there's a simpler approach there and you can tie that with the historical data if it's available.

And coming back to my assumption at the beginning, is total anti-HAV a surrogate marker for anything else? I've submitted that it isn't.

Hep. E we can deal with pretty quickly. I think that the principles that I've talked about for Hep. A are very similar to Hep. E theoretically with one consideration, that there's not a total anti-H -- the assays that are being produced for anti-HEV are class specific, but none of them are FDA approved at this point, and there are some very significant concerns about their specificity,

particularly in nonendemic populations like ours.

And I think, therefore, it's simple at this point that any such documentation, serologic, should be considered unreliable at this point, and so at the present time donors with that history meeting the other criteria for exclusion should be deferred. I use the word "exclude" there, but should be deferred.

And with that, hopefully I've provided some seeds for thought or provocation, and maybe some of you can saw that limb off the tree that I sat down on later on.

Thank you.

DR. TABOR: Thank you very much.

We probably need a technician again to help us with the screen.

While we're waiting for that, let me just raise the issue that in terms of blood donors, as opposed to plasma donors, although when we're talking about blood donors we have to consider that many of those donors will have their plasma used as recovered plasma; in terms of blood donors and exclusion for when they really had Hepatitis A or Hepatitis E, we're talking about a lifetime exclusion for someone who's had a short-lived

disease, universally short-lived disease, and that's something to keep in mind when we talk later.

Again, could I ask for a technician to help change the -- it's the selection screen that needs to be changed. Great. Thank you. Great. Thank you very much.

The next speaker is Dr. Adrian Di Bisceglie. Dr. Di Bisceglie worked for many years as head of the Liver Disease Section at the National Institutes of Health, and his laboratory and our laboratory had many beneficial collaborative research activities over those years.

For the past four or five years or so he's been Associate Chairman of the Department of Internal Medicine at St. Louis University.

Dr. Di Bisceglie is going to be speaking on the significance of hepatitis that is documented not to be due to any of the Hepatitis A through G viruses, but, for instance, a patient who is known to have had documented EB virus or CMV hepatitis in that past.

Dr. Di Bisceglie.

DR. DI BISCEGLIE: Thanks very much, Dr. Tabor.

Well, I'm going to try to be the clean-up here to try to cover everything else that other speakers haven't mentioned, and that's why there's such a long list up here.

This slide lists other infectious agents associated with hepatitis. There are the herpes virus groups or the Magella virus, Epstein-Barr virus, herpes simplex, and we'll come back to some of these in a little more detail as we go through.

Almost all of these viruses causes hepatitis as part of a generalized infection, and the clinical presentation of these patients very often is of a systemic disease rather than specifically of hepatitis.

And on the right-hand side there's a group of even more rare viruses that are associated with liver injury and with hepatitis, some of them things that we are very rarely likely to see in this country, such as Lassa fever.

I think we shouldn't forget that there are nonviral infectious agents that may cause jaundice, bacteria and other organisms. Leptospirosis, for example, comes to mind, typhoid fever, and so on.

Let's talk about Sadam Magella

(phonetic) virus a little bit. There are certain categories of CMV disease. There's congenital CMV infection. This is associated with the presence of hepatosplenomegaly and jaundice in neonates.

There is acute disease that occurs particularly in children. There was a time, I guess, during Harvey Alter's first transfusion studies, when there was a lot written about post-transfusion CMV.

What we deal with a great deal clinically is recrudescence of CMV infection occurring in immunosuppressed hosts, such as after organ transplantation.

Another connection between CMV and liver disease is is there a relationship between sclerosing cholangitis and CMV infection in patients with advanced HIV and AIDS. The diagnosis of CMV infection relies on culture of the organism and histologic appearance.

So here is a liver biopsy, for example, of a patient with CMV hepatitis. These are hepatocytes, the nucleus showing the characteristic intranuclear inclusion of CMV infection.

Infectious mononucleosis next. As part of the disease, one may see hepatomegaly in as many

as ten to 15 percent of patients. Jaundice is less frequent, may occur in up to five percent of patients.

The liver disease is usually mild. There are modest elevations in the amount of transferases and in the alkaline phosphorase (phonetic). The diagnosis is fairly easily made with a monospot or a similar antibody test.

This disease is usually mild and self-limited and really does not go on to cause chronic hepatitis except in very rare situations of immunosuppressed individuals.

Herpes simplex hepatitis. Hepatitis occurs here as part of a disseminated disease, again, in immunosuppressed persons. It may be a rare cause of fulminant hepatitis. It may be treated with acyclovir.

Now, there are one or two papers out there showing that among patients who present for the first time with genital herpes, there are minor elevation of the amount of transferases documented. The patients are rarely jaundiced. So there may be a milder form of herpes simples hepatitis, but again, it's an acute, self-limited disease.

Then there's not much to do except just

list these rare of exotic viruses causing hepatitis: yellow fever, the viral hemorrhagic fevers, and each of these, such as Coxsackie B adenovirus, varicella, rubeola and echovirus, may cause hepatitis. It's all self-limited, and it's extremely rare.

I do want to talk a little bit about unknown forms of hepatitis, idiopathic or Hepatitis X, and I'll divide it up into a discussion of acute hepatitis, fulminant hepatitis, aplastic anemia associated hepatitis, and then chronic liver disease.

You've seen this slide already from Ian Williams. He focused on Hepatitis A and B. I want to focus on the four percent of patients with acute viral hepatitis in the United States where there is no identifiable cause. What is that disease?

Firstly, or extrapolating on those numbers, the CDC has made the following estimates of deaths in the United States from Hepatitis A, the number of cases estimates changes over time. At this time we're 75,000, with a few deaths. Hepatitis B, death was more frequent. In patients with non-A/non-B hepatitis, for want of a better term, Hepatitis X, the number of estimated cases

was 37,500, and some of those were associated with death.

Notice that Hepatitis C is not on this list. Hepatitis C is an extremely rare cause of fulminant hepatic failure.

In Miriam Alter's studies of acute sporadic non-A/non-B hepatitis, she described the features of patients with anti-HCV positive non-A/non-B and compared them to the anti-HCV negative cases. They were comparable with regard to age and gender. The patients with the Hepatitis X were more frequently in the lower socioeconomic groups.

A history of parenteral exposure occurred in some of these patients, but was more common in the HCV positive cases. As we know, HCV infection is very like to go on to chronicity. Hepatitis X, it looked like chronicity did occur. Now, remember that chronicity here is defined as the presence of prolonged elevation of the ALTs because there are no virologic tests. So a small proportion of these patients did have persistently raised ALTs.

Again, continuation of the same studies looking at the risk factors. Parenteral exposure was found in 13 percent of these patients and low

socioeconomic status.

So that's sporadic, and let's talk about the blood transfusion setting a little. These data are slightly old, but at the NIH blood bank Harvey Alter at this time identified 97 cases of post-transfusion hepatitis. Most of them were HCV positive. There were 12 non-C cases.

Interestingly none of these patients were jaundiced, although they all met a biochemical definition of hepatitis as measured by raised ALTs.

Now, I may be the last person in America to hear about the discovery of the new hepatitis virus. I got a press release faxed to my office yesterday about the discovery of something called the SEN-V (phonetic) virus. Harvey Alter was quoted as saying that the test developed by the company tests positive in a substantial proportion of these patients.

I guess we'll wait to see more about that when it appears in scientific journals.

An interesting sideline on that was this press release came from a company called American Standards, who proudly announced that their other products included Trane air conditioners and Armitage Shanks porcelain toilet bowls.

Other studies of post-transfusion hepatitis have also looked at Hepatitis X. Here's Victor Feinman's Canadian study of post-transfusion hepatitis, comparing patients who had received a blood transfusion. I guess comparing those who had received autologous transfusions. The rate of development of Hepatitis C was .21 percent.

Development of Hepatitis X was .55 percent. Interestingly, among those with autologous transfusion it was .61, comparable numbers between the two groups, making one wonder if some of what we call Hepatitis X is not just the background noise associated with being severely ill and requiring a blood transfusion.

The TTV study -- Blaine is here -- looked at HCV versus Hepatitis X, found a comparable incubation period. The liver disease tended to be milder with Hepatitis X, fewer symptoms, no jaundice; again, a small proportion who'd go on to chronicity.

Okay. A few words about fulminant hepatic failure. This slide lists UNOS data showing etiology of fulminant hepatic failure in adult liver transplant patients, and the largest single identifiable group is non-A/non-B hepatitis,

non-A/non-B/non-C Hepatitis X, not identifiable cause.

When one tries to look at viral causes among these patients, this is a study from Richard Sallie looking by PCR for Hepatitis C, B, herpes simples virus, EBV, CMV, and HHV6 in 45 patients with fulminant non-A/non-B, normal controls and transplant controls, and none of them were due to Hepatitis B or C.

Some of the patients tested positive for herpes simples and CMV, but not out of proportion to what was seen in the controlled subjects, suggesting that these known viral agents are not the cause of fulminant non-A/non-B hepatitis.

We had done a similar study in patients transplanted at the University of Michigan. Among 14 patients with fulminant non-A/non-B, all were seronegative by PCR for Hepatitis A -- Hepatitis B, C, E, and A.

Elizabeth Fagan, working in the U.K. at that time, described a syndrome of fulminant non-A/non-B hepatitis occurring in children. She found nine cases, most of them younger than 20 years of age, all British with no obvious parenteral risk factors or exposures, and she saw virus-like

particles in the liver on electron microscopy. Most of them were anti-HCV negative.

Seven of the nine patients underwent liver transplantation and developed recurrent hepatitis in five of the seven.

Now, this observation Dr. Fagan has tried to carry forward to identify a viral agent. I don't believe that has happened yet.

There's a recent paper describing fulminant hepatitis associated with parvo virus B19. This was in Europe. Forty-five children with fulminant hepatic failure were looked at. Of the 45 children, 21 had cryptogenic liver disease, no obvious cause.

Let me see if I can focus this myself. There you go.

Twenty-one had cryptogenic disease. Of these 21, four were positive in serum by PCR for B19, parvo virus B19 DNA. Of the B19 positive cases, four of 11, or 36 percent, were under the age of five years. So these were very young patients developing this fulminant liver disease, but although it was defined as fulminant, it tended to be on the mild side. All of the patients recovered, and again, there was no chronicity

detected in any of these patients.

Aplastic anemia. I'm going to need help focusing that, please. The syndrome is bone narrow aplasia occurring weeks to months after recovery from acute hepatitis. Typically this has been described in young males with no risk factors for acquiring hepatitis. Anemia can be often severe and unremitting, has bee described to occur after liver transplantation as well.

The basis for this is not known. It may be immunologic. Parvo virus, perhaps we should look at parvo virus again as a cause of this syndrome.

Most of these cases cannot be serologically linked to Hepatitis A, B or C. The search for other known viruses has been unrevealing. Chimpanzee transmission studies have been negative.

Neal Young's lab here at NIH has studied this syndrome, and of 28 patients with aplastic anemia and non-A/non-B hepatitis, 36 percent had HCV RNA in serum. However, a lot of that may have been due to blood transfusions to treat their anemia.

Fifty-eight percent were HCV RNA

positive if they had received more than 21 units of blood, and this was less frequent if they'd received less blood.

Of the three livers from patients with fulminant hepatic failure who developed aplastic anemia, none were positive for HCV RNA.

Disease we've read about is syncytial giant cell hepatitis. This is a syndrome of severe hepatitis characterized by the presence of large syncytial giant hepatocytes. Dr. Phillips, who's an electron microscopist, identified intracytoplasmic paramyxovirus-like structures, and found that this disease occurred more commonly in children.

Here's a liver biopsy from such a patient showing these very characteristic hepatocytes with many nuclei, up to 20 of them.

It's not clear that this is an infectious disease. In fact, Bob Purcell and I had taken large volumes of plasma from this very patient and tried to infect chimpanzees unsuccessfully some years ago.

Chronic liver disease. Let's finish off with that. These are data from the CDC looking at Jefferson County in a cross-sectional survey of

patients with liver disease. Seventeen percent of them had cryptogenic liver disease, and that's the group we're going to focus on.

The possible causes of cryptogenic liver disease we don't know, but they may include things like atypical autoimmune hepatitis, patients who don't have the classical serological markers or perhaps unrecognized, inherited or acquired disorders, and then finally perhaps undiscovered viral hepatitis agents, and maybe we should put in there SEN-V perhaps.

Unlikely causes of their cryptogenic liver disease, I believe, are cryptic HBV infection, that is, patients who are negative for surface antigen, and Hepatitis G virus or TTV.

Hepatitis G virus has not been mentioned today, and I have just one slide on it. HGV infection is usually associated with HCV infection. They usually go together in the post-transfusion setting. The viremia of HGV become chronic in almost all cases.

However, chronic hepatitis or raised ALT is rare in patients who have HGV infection alone. So it probably does not cause chronic hepatitis or chronic liver disease. It may cause mild acute

hepatitis.

The TT virus is not the transfusion transmitted virus, but I gather this is the initials of the patient from whom the agent was isolated. It was characterized by workers at Abbott. It has a circular DNA genome about 4,000 base pairs in length. It's a negative stranded genome, particle size 30 to 50. It's not related to any of the known viruses.

It was initially suggested to be parvo virus-like, but these workers found that it's unrelated to previous viruses. It can infect chimpanzees, but probably does not cause hepatitis.

And one of the early papers on TTV DNA came from Roger Williams' group in London looking at testing for TTV DNA in various groups, patients with chronic Hepatitis C, 21 percent positive; chronic Hepatitis B, 20 percent positive. The non-B/non-C group, there were only 13 of them. Thirty-eight percent of them were positive, but it was also found among healthy controls.

I think we've come to the conclusion that TTV does not cause hepatitis.

In summary and conclusion then, we can see that many infectious agents may cause

hepatitis. Some can be diagnosed by serological tests or histological examination, many of them not though. Most cause only acute hepatitis.

If they cause chronic infection, it may occur in the immunosuppressed host or chronic infections not associated with chronic liver disease, and I think the etiology of cryptogenic chronic liver disease up to date remains unknown in a substantial proportion of patients.

Thank you.

DR. TABOR: Thank you very much.

It's interesting to hear your comments on Hepatitis X because that's another area that we need to consider with regard to this question.

The next speaker is Dr. Gary Tegtmeier from the Community Blood Center of Kansas City, who will be speaking on viral marker rates in Kansas City donors with a history of hepatitis.

Dr. Tegtmeier.

DR. TEGTMEIER: Thank you, Dr. Tabor.

Recycling has become a very popular activity in U.S. society, both popular and necessary. In the little community I reside in, we recycle everything, bottles, cans, newspapers, yard waste, even old appliances.

And what I'm about to do here in the next 20 or 25 minutes with you is recycle some very old data because I don't believe there's very much current data on the subject that I'm presenting.

You heard about Ed's studies earlier this morning that were published in the late '70s, early '80s. This data was accumulated on samples collected during the early '80s, and I'm sure Robin scoured the countryside trying to find evidence of contemporary data, but apparently none is available.

Well, I don't think I'm getting the job done here. Oh, you have the magic touch.

This slide is simply to acknowledge my collaborators in this study, many of whom have retired or moved on to new jobs, but they, in fact, were the people who were assisting me in this work.

What I'm showing you here are prospective donors with a history of hepatitis or jaundice deferred at our blood center over the period 1975 to '92, and you can see that between '75 and '84 between 100 and 120 donors a year were deferred for that cause.

1985, that number went to '87, and from '86 forward up to the present, we've been deferring

an average of 60 to 70 donors a year. Actually I think more recently that number has fluctuated between 40 and 60 subsequent to '92.

Just calculating, doing some back of the envelope calculations about the number of donors that one might potentially recover if this requirement to defer donors with a history were removed, unlike my colleague, Dr. Foralice (phonetic), who calculated that the donor loss back in the '70s was about 75 or 77,000 donors a year, my guesstimate extrapolating from our collection data to the country at large would have that number closer to 8,000, or about a 90 percent drop in the period of time from the time Frank's study was done in the '70s.

We studied donors that were accessioned between '82 and '87 who had a history of hepatitis or jaundice which was not neonatal and not associated with infectious mononucleosis. Donors were asked to volunteer a specimen, and of the 522 donors we deferred over that time period, 304, or 58 percent, agreed to provide a sample.

This is how the samples were accessioned by year. We had very nice entry rates in the first couple of years. Then the numbers went down to the

50 to 60 percent range, and then plummeted in '87. I think our donor historians got tired of doing this study and were less zealous in recruiting donors in, but there's 304 of the 522.

There were two males for every female entered in this study, and that gender breakdown reflects the overall gender composition of the 522.

These are unlike Dr. Tabor's study. We used different so-called normal donor populations to compare marker rates in, as seemed appropriate at the time. In 1985, when the study was ongoing we randomly selected 1,000 samples from allogeneic donors, all of the allogeneic donors that were collected in that year.

We selected, in an unselected way, 1,512 donors to do anti-HAV prevalence and ALT prevalence in 1988.

We used first time blood donors in 1990. This represents all of our first time blood donors' allogeneics that year for assessment of ALT rates in that population.

We used first time donors in 1993 specifically to have anti-HCV multi-antigen test data.

And then finally, here are the cohort of

304 donors with a history of hepatitis that were tested for HAV, HBV and HCV markers, as well as ALT.

And in subsequent slides you're not going to see this denominator remain constant. In fact, it will fluctuate, and that's because these donors were tested in real time as they were accessioned. Some samples were QNS, and in the period '82 to '86, we were not doing ALT. We referred samples out, and the laboratory was not 100 percent effective in referring samples out for ALTs. Likewise there were QNS issues.

So this 304 you'll see in a reduced number, but at the end I will summarize data based on a cohort, a sub-cohort of 254 donors on whom we had complete testing.

So this is the prevalence of Hepatitis A in our donors with a history of hepatitis. Forty-eight percent of them tested positive by the test that Dr. Ticehurst described as having moderate sensitivity.

I failed to mention that all of the assays for Hepatitis A and B were either Abbott EIA or RIA assays. The Hepatitis C assays were -- both the screening or confirmatory supplemental assays -

- were the 2.0 version of the Ortho-Chiron test.

So 48 percent of those with a history showed evidence of Hepatitis A. Thirteen, point, two percent of the cohort from 1988 showed evidence. These were donors who were allowed to donate because they gave no history.

I'm moving in the wrong direction here.

This is the prevalence of anti-HBC in donors with a history. A little over 20 percent, or 55 of 269, compared to first time donor prevalence in 1993 donors of 1.9 percent. All of these comparisons are statistically significant by chi square.

We looked at anti-HBS in the 1,000 random donors from 1985 or -- sorry. This is anti-HBC as the only marker of HBV infection. In the cohort from 1985 these obviously were donors who were not being tested for anti-core (phonetic) at the time. One in 1,000 had anti-HBC alone. Four of the 269 donors with a history of hepatitis, or 1.5 percent, showed evidence of anti-HBC alone.

This is not a prevalence of anti-HVS. This is the same 1,000 donored cohort from 1985. Forty-four of 1,000, or 4.4 percent, showed evidence for anti-HBS. Those with a history of

hepatitis, 65 out of 269, or 24 -- a little more than 24 percent.

When we looked at anti-HCV, the comparator population were 1993 first time donors, and this rate of .53 percent represents EIA repeat reactive donors who were either positive by RIBA 2 or indeterminant.

The same criteria were used in terms of measuring HCV exposure rates in donors with a history. Nine, point, four percent of those showed evidence for Hepatitis C exposure.

We took the population, in this case 254 donors with a history, and stratified according to anti-HCV results. Those with a history and no anti-HCV, 41 of 233 had anti-HVC, or 17.6 percent, whereas those with a history of anti and anti-HCV, 11 or 21 or 52 percent were positive for anti-HBC, showing the effective surrogate nature of anti-HBC in identifying HCV positive donors with a history.

Likewise, when we did the same experiment with ALT, we had fewer donors because some were not sent out for ALT, but of the 209 donors with a history and no anti-HCV, 18 or 8l6 percent had elevated ALTs out of 45 cutoff, whereas 15 or 21, or 71 percent had elevated ALTs on that

same cutoff.

Finally, looking at elevated ALTs in the population at large, those with no history, that is, first time donors from 1990 had a cutoff of 45. Five hundred and six out of 10,755, or 4.7 percent, showed evidence of elevated ALT. The population, 254 hepatitis history donors, 44 of them, or 17.4 percent, had ALTs above 45.

Now, this is the cohort I mentioned, the cohort of 254 on whom complete testing was available, and this is the straight look at the marker rates. Fifty percent had HAV. Twenty-six percent had evidence of HBV, and 12 percent had evidence of HCV, and a third of them had no evidence of either Hepatitis A, B or C.

Note the high prevalence of males relative to females in each of these categories.

Now, obviously these numbers don't add up to 100. So some of these donors had to have multiple exposures, and this is the breakdown in terms of marker exposures across the 254 in relation also to ALT elevations in each of the categories.

So there were 83 donors with no serologic evidence of A, B, or C. Sixteen of

those, or 19 percent, had ALTs above 45. HAV, 93 donors, eight percent had ALTs above 45. This is not different, significantly different, from first time blood donors. HBV, two of 25, again, the relative elevations here are no different from first time blood donors. Seven of ten with HCV alone had evidence of raised ALTs. Two donors with evidence or 25 donors with evidence of A and B. Only one had a raised ALT. Three donors with evidence of A and C infection. Two had raised ALTs, and then ten donors with dual infections, B and C. Five had raised ALT. Five lucky donors had a three bagger, trifacta. Four of five had raised ALTs.

So overall this is the 44 out of 254, or 17 percent, of the cohort with raised ALTs, and, again, none are sixfold higher represented with ALTs in this population.

This is just in an overall comparison, rapid, HAV between donors with a history versus no history. Forty-seven percent versus 13 percent; I didn't show you the HBSAG. This is out rate in first time donors. This was the rate in the hepatitis history cohort. Anti-HVC, 20.4 versus 1.9; 24.2 versus 4.4 for anti-HVS; 9.4 versus .53

for anti-HCV; 17.4 versus 4.7, elevated ALTS. All of these differences are statistically significant.

Now, there was a time when we were allowed to take donors who had a history of hepatitis or jaundice associate with infectious mononucleosis. That was at some point that I'm not entirely sure of prohibited.

We were able to get some samples from donors who elicited that history, and this was a history they volunteered, not one that we were attempting to elicit from them. And so over the years '84 to '89, we were above to collect samples on 49 such donors. You can see by the bottom line here only four percent evidence of HAV. None was positive for HBSAG. Two showed evidence of -- two percent showed evidence of anti-HVC, six percent with anti-HBS. These were independent, not overlapping here.

And three of the 41 we had ALTs run on had ALTs above 45; again, not significantly different from first time donors.

So in summary, we found that donors with a history of hepatitis are more likely to be male, and although I didn't show the data, older than first time donors. They showed much higher rates

of exposure to both Hepatitis A, Hepatitis B, and Hepatitis C. They showed a greater evidence of chronic hepatitis infection as measured by elevated ALTs.

Those with evidence of HCV exposure showed high rates of surrogate markers for non-A/non-B hepatitis and evidence on chronic infection, and certainly the FDA policy that mandated permanent deferral of donors with a history of hepatitis was a sound one before the advent of multi-antigen tests for anti-HCV. Clearly Hepatitis C transmission was prevented.

We found that donors with a history of hepatitis and anti-HAV are indistinguishable from prospective first time donors who do donate.

Finally, donors who had a history of hepatitis associated with infectious mono. we found had marker rates comparable to prospective donors who are allowed to donate or who do complete the donation process, and so we conclude that donors with a history of hepatitis after the age of ten who show evidence of prior exposure to HAV should be allowed to donate, and likewise donors with a history of hepatitis associated with infectious mono. we believe should also be allowed to donate.

And that concludes my presentation.

DR. TABOR: Thank you very much, Dr. Tegtmeier, for taking another look at that data for the purpose of this conference. It is much appreciated.

I think even though we're scheduled for lunch, and I'm a great believer in coffee breaks and lunch, I think it would be a mistake not to have some discussion before we go to lunch. So I wonder if we could have ten or 15 minutes of discussion on this morning's presentations.

If anyone has any questions or comments, please step up to the microphone. Harvey Alter.

DR. ALTER: Adrian, this is addressed to you. A recent article in the New England Journal and a lot of literature in presentations recently indicate that cryptic HBV is much more prevalent than we thought, certain than I thought, finding HBV DNA in liver and in serum by nested PCR in patients who are HBSAG negative. A lot of that is associated with HCV and implications that it makes HCV worse, but also possibly the cause of Hepatitis X, if you will.

You sort of dismissed that, and I was wondering why. I hope you're right.

DR. DI BISCEGLIE: This is an ongoing story, I guess, for the last ten or 15 years, I think the finding of Hepatitis B, D, and A in serum or liver tissue of patients with various liver diseases. I guess the article that you're referring to looked at a group of patients in Italy doing PCR in their serum and finding it in about 20 or 30 percent of the patients.

I think the data in that paper that the Hepatitis C was worse was really not very compelling and not convincing.

The reason why I've kind of dismissed it is I think for every paper that's published on this subject showing HBV DNA, there probably are several with negative findings, and in my own experience in my lab, we've tested many, many patients with Hepatitis C and cryptic liver disease and not been able to find HBV DNA reliably. I think the assay is a tricky one to deal with.

For example, with Brian McMahon in Alaska, we've tested a lot of anti-core alone positive individuals and not been able to reliably find HBV DNA by PCR.

So I guess I'm just not convinced by the data, but it's a question that's been out there for

a long time and, I think, still remains unresolved.

DR. TABOR: I think it's important to mention there are a number of variables connected with any study of silent or cryptic HBV. There are population variables that we haven't really got a handle on yet that may differ geographically, and also the different use -- use of different primers from different parts of the virus could make a difference.

But I think before I take your question, Blaine, I think what's important in what you're saying, Adrian, is that there is a segment in the donor population or in the infected donor population that might be missed. Isn't that what you're saying, regardless of whether it's cryptic HBV or not?

Hepatitis X would be missed and --

DR. DI BISCEGLIE: (Inaudible.)

DR. TABOR: Right, and just in case anyone can't hear that, what he said was even though we know there's a segment with Hepatitis X, we don't know whether they would give the answer yes to the question have you had clinical hepatitis.

Dr. Hollinger.

DR. HOLLINGER: Well, just one more comment on this. I guess the missing or the big question in these questions about the HBV DNA found in liver tissue and so on is whether the blood is really infectious or not. The fact that you find DNA or pieces of DNA doesn't necessarily mean you have infectious material present, and I think that needs to be demonstrated.

The question is Dr. Williams presents very interesting data at the end of his talk, which went very rapidly, and even I couldn't follow the last three slides, but I think they're critical slides, and I wonder if he could show those again and perhaps go over that data once again because it's, I think, germane to this conference.

DR. TABOR: That's great. Dr. Williams?

DR. WILLIAMS: Sure. Could you cue up my last couple of slides there? It's the one with just three slides in it, four slides in it.

(Pause in proceedings.)

DR. TABOR: While we're waiting for those, why don't you wait up here? Let's see if we have anymore questions or discussion while we're waiting for those.

Dr. Epstein.

DR. EPSTEIN: Thank you.

A question for Gary Tegtmeier. Gary, I guess I was impressed by the finding of an increased ALT of 17.4 percent in those with a history of hepatitis compared with 4.7 percent with a negative history of hepatitis, and I wonder in the group with elevated ALT, can you comment what percent in each category were negative for all of the testable markers? Because that's the group that would represent the threat to the blood supply presumably.

I may have missed it, but --

DR. TABOR: I am sorry. No one is hearing the conversation. If it's possible for both of you to go to microphones. There is a microphone right behind you.

DR. EPSTEIN: Again, the question is whether we have the negative marker rate in the subset that had elevated ALT.

DR. TEGTMEIER: That was 17.4 percent

DR. EPSTEIN: No, I thought 17.4 percent was the percent elevated ALT with a positive history, and you're saying that also 70 percent of those have no markers.

DR. TEGTMEIER: Sixteen of 83, Jay, that

showed no serologic evidence but elicited a history had raised ALTs at a cutoff of 45.

DR. EPSTEIN: I'm sorry. Maybe I'm not following, but of those with ALT elevation --

DR. TEGTMEIER: There were 83 donors with a history of hepatitis who showed no evidence, serologic evidence, for Hepatitis A, B, or C, and of that 83, 16 had raised ALTs at a cutoff of .5. Is that the question you're asking?

DR. EPSTEIN: Okay, and how about those with negative histories? What percent with ALT had negative marker?

DR. TEGTMEIER: What percent with a negative history?

DR. EPSTEIN: Right, but a raised ALT also had negative markers.

DR. TEGTMEIER: Well, that was 4.7 percent. That was a population of first time donors who presented and were allowed to donate, and that at a cutoff of 45, 4.7 of those donors had raised ALTs.

DR. EPSTEIN: No, but I'm asking of those with raised ALTs, what percent had negative markers?

DR. TEGTMEIER: Okay. I don't know the

answer to that. I can get the answer to that, but it certainly is a minority of the group. I can't put a number on it. I don't have that with me, but we can certainly -- I don't have the data here.

DR. EPSTEIN: Okay.

DR. TABOR: Before we get to these slides, let's take one question from Dr. Hewitt.

DR. HEWITT: Thank you.

Patricia Hewitt from London, U.K.

I think it's a comment rather than a question to Dr. Tegtmeier.

You showed the rates of raise ALT in donors who had a history of hepatitis and had Hepatitis C markers and equated that with chronic liver disease. I wonder if when we looked at a group of donors who had evidence of Hepatitis C infection and raised ALTs, in the majority of those donors it was due to alcohol intake, not chronic liver disease. They had actually replaced one behavior, which was intravenous drug use with another behavior, which was alcohol intake.

And I just think there is a danger in equating raised ALT with chronic liver disease until you've eliminated other reasons for a raise ALT.

PARTICIPANT: (Inaudible.)

DR. HEWITT: When we saw alcohol to donors who were Hepatitis C infected and had a raised ALT and counseled them about alcohol intake, a significant proportion reverted to a normal ALT on reducing their alcohol.

DR. TABOR: Dr. Koff.

DR. KOFF: I'd also like to ask Gary. One of the major causes of an ALT that we see in our not necessarily donor population, but certainly also in donors, is an increased body mass index. There seems to be a very good correlation of obesity if you separate all the other things.

Do you have any data? Obviously the numbers are getting smaller and smaller, but I wonder if you have looked at that.

DR. TEGTMEIER: We have not. In theory we could do that since the FDA requires us to keep records forever. We could go back to the history sheets and look at donor weights. That's a good suggestion. Thank you.

DR. TABOR: Dr. Kleinman.

DR. KLEINMAN: Yeah, just to follow up on that, I think, because Jay obviously was trying to compare those two pieces of data and attaching

potential significance to preventing Hepatitis X, I suppose, but again, your ALT data in the group with history of hepatitis, that group is two thirds male, and your control group is probably not two thirds male, and so I think there are a lot of other reasons.

Since you don't have a direct control group that's matched for other demographic variables, it's very dangerous to make ALT comparisons because we know demographics have a big influence on ALT levels.

So if you do go back to get the data, you'd have to control it, I think, quite carefully for it to be meaningful.

DR. TABOR: Dr. Rottacheir (phonetic).

PARTICIPANT: Yeah, I also --

DR. TABOR: Could you speak a little louder into the microphone please?

PARTICIPANT: Yeah. I have one question for you, that you mention in your slides that recently the number of cases for (unintelligible) is decreases. Do you have any guess why?

DR. WILLIAMS: I don't think anyone knows for sure why the number of Hepatitis C cases have been decreasing, but I'll make some guesses

for you.

One optimistic guess is that in the U.S. Hepatitis C predominantly is transmitted through injecting drug use and sex. People are finally getting the messages we've been telling them about HIV, using clean needles, needle exchange, all of those sort of things that we've been saying. That may have something to do with it. That's an optimistic viewpoint.

I think the pessimistic viewpoint is that Hepatitis C has pretty much spread through the injecting drug using community. Anybody who injects drugs is pretty much already infected with Hepatitis C, and this is something that's happened over the last 20 or 30 years.

And there's evidence from a couple of sources to support that. So what we had is Hepatitis C starting to be spread widely through the U.S. through the '60s and '70s, predominantly driven by injecting drug use which spread widely through the community and basically it sucked up all of the susceptibles, and all we have left are a very handful of people out there who can only get infected.

So basically we've run out of people who

can get Hepatitis C in that group.

Is that an adequate explanation?

Okay. Ray, sure.

DR. KOFF: The other thing you said, Ian, is that you thought this was a relatively new disease, and my recollection is, and Ed may know, weren't there studies done of immune globulin made in the 1940s in the United States which, when we tested for Hepatitis C antibodies were, in fact, found to be positive?

DR. WILLIAMS: Maybe I was sort of -- I think a new disease in terms of newly spread through the community. This is a --

DR. KOFF: So you used the term "emerging." This is an "emerging"?

DR. WILLIAMS: It emerged is the problem. It emerged through the '60s and '70s and early '80s, and it's demerging now because it's basically burned out all of the people that are susceptible for this, and with the increasing blood safety, we've basically eliminated the people who would have been at risk in the general community, and all that are left are people that are at high risk, which are mainly injecting drug users.

So it's emerged and we're all left with

-- okay. For a couple of minutes on this slide, I thought I'd run back through the last two or three slides.

This is the NHANES data which puts Hepatitis A, B, and C on one slide maybe. And the reason I put this slide us is I think one important point is that a likely cause of hepatitis at any age regardless is Hepatitis A, especially people under 20. If you had to choose the likely cause of hepatitis, it's almost always going to be Hepatitis A in kids, especially people under 20. That's the first point.

And on some of these other slides, what I did basically is in our sentinel county study, which is people with acute viral hepatitis, I sub-selected a group of patients, namely those with acute Hepatitis A, and the reason I did that is people with acute Hepatitis A are most likely to be like blood donors or people you would see. So they're a pretty good cross-section of the general population.

Among these people, we asked them, "Have you ever had hepatitis before? Do you have a previously history of hepatitis?"

And the bottom line is very few people

report histories of hepatitis. Less than five percent of people between 20 and 30, and it's around eight percent of people older than 40. So very few people actually report history.

However, if you look at who has serologic markers, a lot more people have serologic markers than actually report history, and by the time you get up to 40 years of age, roughly 25 percent of people have serologic markets of either Hepatitis B or Hepatitis C, and again, remember only about eight percent of people actually reported having any history.

So the final question is: so if you do report a history, how accurate are you in terms of recalling Hepatitis B or C?

Well, basically you can't look at the people under 20 because there's only one person who reported a history. So you can kind of ignore the far left bar. However, there's reasonable numbers in those 20 to 30 and over 40.

Among those 20 to 30 or 20 to 40, most people did a pretty good job of recalling their history of hepatitis was actually Hepatitis B or Hepatitis C. We don't know about this bottom chart here where there's no history or no serologic

history. This could have been EBV or be something else, although most people who do report a history, it's Hepatitis B or C.

It gets even better in people over 40. Almost all people who report a history had either B or C, and very few of them had something else or nothing at all.

Are there any questions on those data since I did it real quickly?

DR. TABOR: Yeah, could you just go back a couple of slides? Okay. Stop right there. This is the proportion of -- you identified people with acute Hepatitis A.

DR. WILLIAMS: Yeah.

DR. TABOR: And then asked them if they had ever had a history of hepatitis before that?

DR. WILLIAMS: Yes.

DR. TABOR: I see.

DR. WILLIAMS: John?

These are acute Hepatitis A patients. IgM, anti -- should be positive, jaundiced. They have jaundice. They're sitting in front of you, and you ask them about previous hepatitis, and the reason I selected this group is we don't have health controls. We don't have anybody else we

asked this question of.

And the reason I separated A from B and C is because people with Hepatitis B and C in the sentinel counties are vastly different than people who are going to come see you in a blood bank. They're injecting drug users. They're men who have sex with me. They're really a high risk population.

Hepatitis A as a whole are pretty low risk people. They're a pretty good cross-section of the general population in our counties.

Sir?

PARTICIPANT: Have you taken data from your sentinel counties and looked at it the other way? In other words, if you did the screening, the test that would normally be performed at blood banks, how many are left over that you wouldn't screen out who still report a history of hepatitis?

DR. WILLIAMS: See, the problem is all we have are people that are acute case. We don't have anybody who's not bright yellow sitting in front of us essentially.

PARTICIPANT: So do I understand you're saying you would find them all by the screening?

DR. WILLIAMS: No. We'd basically find

them because they're acute, symptomatic, and reported to us.

PARTICIPANT: Oh, but you haven't done it the other way?

DR. WILLIAMS: Because we can't, because they either have Hepatitis A, B, or C when they come to see us. So they are already acutely ill. So that's why only sub-selected Hepatitis A.

Is that clear?

DR. TABOR: That's clear.

Could you advance the next slide? And these are the same people as in the previous slide who have markers.

DR. WILLIAMS: Yeah.

DR. TABOR: If I understand this correctly, everybody in these bars has a history or, no, they all have Hepatitis A. Almost no one had a history because that was a previous slide.

Hit the wrong one.

DR. WILLIAMS: Yes, no one has history of Hepatitis A.

DR. TABOR: Okay. So the question is within this little group who have a history of hepatitis, how many with no markers are you going to detect.

DR. WILLIAMS: No, the next slide is how many of everybody has markers, whether or not they report history.

DR. TABOR: Right, but in terms of the question we're trying to answer today --

DR. WILLIAMS: It's the third one.

DR. TABOR: -- it's the third one.

DR. WILLIAMS: If you report a history, how many of them have --

DR. TABOR: This one?

DR. WILLIAMS: Yeah. If you report a history, how many of them have markers of hepatitis, at least B and C? You have to sort of ignore this because there's only one person in this bar.

DR. TABOR: So in terms of the question we're asking today, are we asking about this portion?

DR. WILLIAMS: Basically the question --

DR. TABOR: In other words, how many people are we picking up that would not be picked up by serologic tests, by this question, "Have you had hepatitis?"

DR. WILLIAMS: You would pick up this proportion of the bar.

DR. TABOR: But these are all people with markers.

DR. WILLIAMS: These are all people -- so you --

DR. TABOR: So we're already picking them up?

DR. WILLIAMS: Picking those folks up, yes.

DR. TABOR: So the question today is: with the question have you had clinical hepatitis, are we picking up anyone in this portion of the bar on the slide?

DR. WILLIAMS: The answer would be, no, because they don't have any -- they may have had something else, but it's not Hepatitis B or C. So it's a little --

DR. TABOR: Well, the point I was trying to make though, if I've understood the slide right is not that the answer is no, but the question is: do we pick up any other types of hepatitis or people without markers, but who have Hepatitis B or C in this portion of the column.

Dr. Alter.

DR. ALTER: Yeah, I was actually sent by the cafeteria. They've been waiting for us.

I want to answer John Finlayson's (phonetic) question.

DR. TABOR: Is that true that the cafeteria --

DR. ALTER: No, no, no.

DR. TABOR: We'll stop after you question and Dr. Ticehurst's question.

DR. ALTER: I'm only kidding.

In answer to John's question, you know, we do this. We go backwards in people who have markers of Hepatitis C and have looked at hundreds and hundreds and hundreds of these people, and virtually none of them have a history of hepatitis. So it's just rare that in people with known markers to find a history, and I think it's true even in B, although less so, less dramatically.

DR. TABOR: Dr. Ticehurst.

DR. TICEHURST: Just a point of clarification and then a question. Should this slide on the red box, should that say "no markers"?

The question is I'm a bit confused. These are people that have acute Hep. A. So they can't have a history of acute -- they can't have a history of acute Hepatitis A by definition. So does that confound the analysis?

PARTICIPANT: (Inaudible.)

DR. TICEHURST: I just am not sure I understand how these data -- I understand they answer the question with regard to B and C, but I don't understand how they answer the question with regard to the correlation between a history and whether that history is truly Hep. A.

PARTICIPANT: (Inaudible.)

DR. TABOR: Let's break for lunch and try to be back around 1:15.

Thank you.

(Whereupon, at 12:13 p.m., the meeting was recessed for lunch, to reconvene at 1:15 p.m., the same day.)

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

(1:15 p.m.)

DR. BISWAS: On the agenda we now have industry presentations on the issue. We would like to get the views of the blood organizations on the question, history of hepatitis.

So the first one to speak will be Rebecca Haley, Dr. Rebecca Haley, from the American Red Cross.

DR. HALEY: There. I think it's going to work. That's great.

I'd like to thank Dr. Biswas for organizing this conference and for giving us a chance to talk about this problem because we feel like that we are leaving a lot of donors behind when we could be using them to make the blood supply safe and plentiful.

Now, plentiful is getting to be more and more of a problem with the things that have come up in the last number of months. Now, if we do a deferral of the donors who have lived in Great Britain for more than six months, within a period of time that is going to be another big hit on the donor population.

So let's go through what this problem

looks like from the donor perspective.

The issue is that donors give a history, a distant history of more than one year ago, and that's the way we're going to approach this; a history of more than one year ago of jaundice or hepatitis, and then they are indefinitely deferred as blood donors if that happened after age 11. Is this appropriate?

We don't think so. We'd like to thy to convince you that perhaps it is not. What we're going to talk about here is Hepatitis A, B, C, Epstein-Barr virus, cytomegalovirus, and then some other unknown disease syndromes, many of which have been discussed this morning.

My disease list will not be nearly as exhaustive as our experts and our hepatologist.

This is a table from the Schreiber, et al., paper in the New England Journal of Medicine estimating the risk of hepatitis for donors collected in the window period by figuring backwards from what has been observed over the years, and there are a number of authors of this paper in this audience today.

And now remember the 54 to 192 days for HCV and the 37 to 187 days, which we considered to

be the window period length for these two viruses because we'll come back to it.

Okay. The number of donors affected: how big is this problem? In the American Red Cross, donors deferred by history and put into our DDR total today 247,704. So that, we think, is a considerable hit on the donor population. We don't know how many of these donors we could get back today, but these are history only people, people who have a history of jaundice that's sort of nonspecific after age 11. They don't know what or people who have history of a specific hepatitis, which we cannot at this point take.

Indefinite deferral is required, and if you have Hepatitis A about 90 days after confirmed Hepatitis A, you will probably be or our experts this morning told us that you would be -- and other public health individuals say -- you would be out of the woods; that these people would no longer have a risk of being antigenemic, and if you had an IgM that was positive at the time that the donor was ill or if you had an IgG anti-Hepatitis A incidental finding at some later time, if a sufficient amount of time has passed since the observed disease or the observed exposure, then you

should be safe as a donor because this is not carried long term.

What about Hepatitis B? Well, current regulations say indefinite deferral required for disease, Hepatitis B history or history of jaundice in febrile illness after age 11, and we've heard that if you were born in the United States or even in some other countries if you were significantly ill after age 11, the older you are, the higher the possibility is that your hepatitis would be something other than Hepatitis A.

The donor we would expect to seroconvert to Hepatitis B surface antigen positive or anti-Hepatitis B core certainly within one year -- that's a generous margin -- were the 37 to 87 day window period for this particular seroconversion.

So if you're positive for anti-Hepatitis B surface antigen but negative for the other markers and it has been a year, we think that you would be acceptable as a donor.

Okay, and there was the case mentioned this morning of perhaps co-existence of anti-Hepatitis B and Hepatitis B antigenemia. We saw that very clearly when we started doing octolony (phonetic) plates a very long time ago, and some

donors did have both at the same time.

We still don't know what the means in the context of infectiousness, but they certainly would be deferred permanently in our system.

Indefinite deferral is required for history of Hepatitis C. Perhaps included in the jaundice and febrile illness that we've talked about before, again, we think that one year would allow for seroconversion, and of course, all of this does not take into account the NAD testing that we're not doing that we think has shortened the window period considerably.

We're currently seeing a rate of approximately one in 200,000 donors, and I've been on vacation for about two weeks so I can't tell you if that's changed or not, but that looks like that we're picking up about one in 200,000 donors with a Hepatitis C nucleic acid test. So that would shorten this even more.

But taking this very conservative estimate of 54 to 192 days and a history of HCV, if it was more than one year before donation with negative tests, we don't think this poses any greater risk.

Now, here we are going to get into the

fringe territory of a number of donors that we've had to defer because we're told that Epstein-Barr and CMV you can accept only if you can prove that there was absolutely no other hepatitis. Well, most people are not treated in that way when they come down with Epstein-Barr virus. They say, "I have a sore throat," and then they have jaundice. They have fever. They feel terrible, and the doctor does a heterophile or a monospot and says, "You have mono. You're fine. You know, go and lie down for a while," which is very hard to do with the late teenage and early 20s people who tend to get rip-roaring cases of this, but then they recover, and they don't show different hepatitis transmittance rates if they've have that complication with EBV or CMV than other donors who had that same disease without this, and we often don't have evidence that would hold up in a court of law or a complete work-up that say that that was the only thing we had. We just have the diagnosis of the physician and the word of the patient, which now would be our donor.

So we would say that these people are certainly relatively safe.

Well, scattered into this we also have

some malaria. Malaria itself is screened out by alternate questions, but these people often get deferred. They say, "Well, you know, I was in the Peace Corps, and I had jaundice, and I was sick."

And they say, "Well, did you have malaria?"

"Well, I don't know. There wasn't a doctor nearby."

Well, those people wind up in our deferral registry.

People say, "Well, yeah, I was jaundiced. My knee was infected, and I was jaundiced."

And then we question more closely and find that they had erythromycin or they had another antibiotic.

Gilbert's syndrome certainly takes a toll because they're typically people who are often examined by physicians or have observant parents, and they find out that they have Gilbert's, and they say, "Yes, I get jaundiced," and so they wind up in our deferred donors.

So none of the others require deferral. Also the jaundices of pregnancy often wind up in this category.

So our recommendation is that one year would capture the window risk period situations, and if we ask, "In the past year have you been diagnosed with or been in contact with anyone diagnosed with hepatitis?" that a yes, we would defer them, keep them in our deferral database for one year, and then testing is the reliable method of screening out infectious donors after the window period.

That is the assumption we have there. That's what all of our incidence data are based on from all the speakers before, except for the Hepatitis X, which I must admit that I don't understand completely.

So along with the other blood donation organizations, we do think a change is in order. We think that these donors would be safe, and that was what we would propose.

Thank you.

DR. BISWAS: Thank you very much, Dr. Haley.

Next will be Dr. Steven Kleinman from the American Association of Blood Banks.

DR. KLEINMAN: Thanks, Robin.

Thanks. Technologically complex up

here.

Well, I'd like to thank Dr. Biswas and the organizers for inviting me today, and I'd like to give the American Association of Blood Banks' position on donor questioning.

So I think the general point here is that we need to adopt a policy based on the current risks and not the historical risks, and this has been well reviewed this morning. In the 1960s when these policies or when this question was first put into place, we had a very high rate of post-transfusion hepatitis, and we had no laboratory screening tests to detect that.

Then I think as was summarized again this morning, we move into the early 1980s when there was a lot of discussion about whether the question should be revised both here at the FDA and BPAC, and also a number of papers published, very interesting international forum in Vox Sanguinis, which I read before this, published in 1981, which I think has a lot of pertinent comments to today.

And so this was talked about, but at that time there was a moderate rate of post-transfusion hepatitis, and the consensus opinion was since most of that was non-A/non-B and we had

no screening test for non-A/non-B, we should continue with the deferral for a lifetime history of hepatitis.

As I mentioned, a number of writers at that time said, "However, once we get a screening tests for non-A/non-B hepatitis, we don't see why the historical questioning would need to be kept in place."

So this gets us to the situation that we find ourselves in in 1999, where we know the rate of post-transfusion hepatitis is exceedingly low. We can project it by mathematical models. We haven't been able to measure it very accurately because we can't study that many patients.

What would the causes of post-transfusion hepatitis be in the current era? Well, we could still transmit Hepatitis B and Hepatitis C, but the only real possible transmissions that we know of would be window period transmissions. With respect to Hepatitis B, those tail end transmissions that Dr. Tabor was referring to would now be, as far as we know, picked up by anti-core testing, which we've been doing for the past ten years, and with regard to HCV, the preliminary nucleic acid testing data that we have from across

the world indicate that chronic antibody-negative transmission is very rare. So essentially our anti-HCV test picks up everybody who's not in the window, and we, as well, now have HCV nucleic acid testing which we know it's being done under IND and is not a required test. Nevertheless, we are deriving the benefit of performing that test, and preliminary data which I'll go into is telling us that we've improved safety with regard to Hepatitis C.

So that's the second point here, that sensitive screening assays now exist.

So to look at each one of these causes a little bit more closely, what is our risk of transmitting Hepatitis B by transfusion today? Well, the Red's estimate is about a 56 day mean window period. You saw on the last slide that the range was about 37 to 90 days. These ranges are based on small numbers of people. So we don't know if that's exactly correct.

And the estimate for transmission is somewhere between one in 65,000 to one in 200,000 cases in the HBV window period. So we think that's still going on today. We're not yet doing HBV DNA testing, and that's occurring presumably in the

context of asking the history question.

So I suppose the question we would have to answer is if we don't answer the history question, would we get any more transmission, and I'll get into that in a moment.

For HCV, for the antibody test, we have a 70 day mean window period. The data, I think, are quite strong that would pool nucleic acid testing at least from results of seroconversion panels and post-transfusion studies.

We will shorten that window from 14 to 21 days, and we currently have a risk of about one in 100,000 per unit risk prior to doing nucleic acid testing, but we're estimating that risk will go down to one in half a million. So the risks of Hepatitis B and C are quite low these days.

Now, Hepatitis A I don't have a slide on. Just to say we know that it occurs. It's, again, very, very rare, still probably worthy of reporting. If you find a case, you can probably still get it published, and we know there's no chronic carrier state, and we know that donations would have to occur in a very narrow window where the patient was viremic and not yet symptomatic, and there is really not good estimates on how long

that lasts, but it's probably only in the range -- the few data that are out there suggest it's only in the range of about a week or so.

So I don't think once you have a history of hepatitis you no longer will transmit Hepatitis A. So we're not going to pick up that person who's currently transmitting Hepatitis A, that rare person, by our current history question because once the answer is -- because if he's a transmitter, his answer would be, "No, I don't have a history of hepatitis," unless he had some previous episode of another hepatitis virus.

Now, for non-A/non-E, which this morning we heard called Hepatitis X, and actually if we do have a new hepatitis virus sequentially it would go from G to H, and then we'd have HHV, but we already have eight of those already or maybe nine, herpes viruses that are called HHV. So it's an interesting nomenclature question, what the next hepatitis virus will be called.

Anyway, I'll call it non-A/non-E right now. Now, what is the risk of transmitting non-A/non-E in 1999? Well, we don't really know. There are no large scale studies and no good way to measure this. We do know that Harvey Alter is

continuing with his NIH clinical center study, and in somewhere between 500 and 1,000 patients, and he may update us a little bit later on the panel. He's had either none or one case of something that might be non-A/non-E.

Now, obviously that's not a lot of patients to follow, but I think we can say that the risk is low.

And if we go back to the historical series of non-A/non-E that Harvey and other people have reported, and we've seen that data this morning, the cases of hepatitis caused in these people are mild. They rarely get any long term sequelae, although we have seen some data to suggest that maybe about ten percent of them go on to chronic ALT elevation. We don't have any real data to suggest that it's those same people with non-A/non-E that actually get into severe liver disease.

And I think maybe more importantly for the question on the table is at least in the post-transfusion series that Harvey had in the past, these people were all picked up by serial ALT monitoring and were clinically asymptomatic. So a history of hepatitis would not be elicited from

these people at least based on their non-A to E hepatitis.

Again, could they have another type of hepatitis in the past? That's possible.

Also, from data from the sentinel county studies, at least the paper that was published on Hepatitis G several years ago, it looks like these people have a strange epidemiology. They look different than Hepatitis B and C, and the conclusion made by the CDC authors is that many of these people probably aren't viral hepatitis because they don't have the profile of an agent that would be spread as are other hepatitis agents.

So I think looking at the data, we would have to conclude that although some of those cases presented as symptomatic cases in the sentinel county studies, they aren't necessarily non-A to E hepatitis.

So the facts that we then need to consider with that background with regard to donor deferral is the current low risk of post-transfusion hepatitis the fact that the history of clinical disease, as we've heard very clearly this morning, is not very sensitive for picking up carriers; it's also not very specific. We already

have a question on the donor history that asks donors whether they've had a major illness or been under a doctor's care in the last 12 months, and I would submit that an acute case of viral hepatitis ought to solicit a yes answer to that question. If we're relying on that question for other acute illnesses, it seems to me reasonable that we don't have to single that question out for hepatitis to still get that history of the last 12 months.

We know that the current question will currently defer donors who are safe because the majority of donors who would say yes and actually had viral hepatitis would have Hepatitis A. We also have heard about CMV and EBV, historical donors being deferred, and I'm sure many donors who answer yes to this question have nonviral causes for their hepatitis.

Another factor that I would like to put on the table is that I think most people now agree there is a need to simplify the donor questionnaire. It's gotten to be extremely long, and we really need to begin to focus on questions that increase safety and eliminate questions whose safety contribution can't be demonstrated or are extremely negligible.

So with that I give you the AABB position, which is that instead of trying to refine this question and fine tune it and look for additional documentation, let's get rid of it. It's not accomplishing anything anymore. It's not protecting recipients. We certainly can't document that it's protecting recipients. The disease burden that is potentially out there is extremely small.

I would submit that we will never be able to get rid of a question if we have to document it in advance, that taking it away will not make things worse because the only way you know is by taking it away. You can't do the study.

So I think we have about as good information as we're going to get about any donor question; that this one is not particularly helpful at this point.

So recipient safety, in my opinion, would not be compromised, and we would be able to reinstate or use blood from some safe donors, and I think Dr. Bianco will give us some figures as to how many donors a little later on.

So in my last slide, I just wanted to raise a few additional questions that are not the

subject of this workshop, but that are related to hepatitis, and I think are issues about deferral that have not been totally worked out, I think, amongst the blood community or perhaps by FDA.

And that is one thing that I raised in the question period this morning, is that what should the criteria for acceptance or deferral of donors be who have had ear or body piercing in the last 12 months. We know that these people are now deferred unless -- and this is where I think it's a bit unclear -- it can be demonstrated that these procedures were done sterilely, and the point I was making this morning is this affects a lot of donors.

I'm not suggesting we should take them all. I'm just suggesting we should have some way in which we can determine in a uniform fashion whether such a donor is safe or not safe, and that way should be something that is not so administratively complex and so tied up in the CGNP process that we can't actually implement it in the normal blood setting.

Another question is if we do take the question away for history of hepatitis, what do we do about the question that concerns close contact

with a person who's had viral hepatitis in the past 12 months, and since that is a mode of transmission, it's not clear to me exactly what should be done, and maybe we can talk about this in the panel discussion.

And finally, something that the BPAC has discussed previously is what about deferring somebody who's had sexual contact with an HCV positive person in the past 12 months. Now, here I want to be more conservative than I think people have generally been because my interpretation of FDA's policy up till now when they reviewed it is you don't need to defer such a person, and yet we hear that sexual transmission is the way that 20 percent, at least according to CDC, of HCV is spread.

And so I think that I'm actually more concerned about this latter fact than I am about some of the others, and again, I don't know that I'm right about this, but I think it would be a good topic if we get a little broader in the discussion that we could go over.

So my purpose for putting up these last three questions is to get people thinking and maybe if we can, come to some debate and hopefully some

agreement about the history of viral hepatitis and we can use the opportunity to go on and start thinking about some of the other related questions.

Thank you.

DR. BISWAS: Thank you, Dr. Kleinman.

And next is Celso Bianco from the America's Blood Centers.

DR. BIANCO: Thank you very much for allowing us to discuss this subject.

I want to talk a little bit about medical history and history of hepatitis and give you some data on the impact of each one of those what we call deferrals in the blood supply.

Medical history in the past in the early days, this was it. There were no screening assays, except for blood typing to insure the safety of transfusions. The history of infectious diseases focused on hepatitis, and we know also that, for instance, in studies that were done in New York in the '50s, 25 percent of patients that received multiple blood transfusions developed clinical evidence of hepatitis.

Today medical history is quite different. It's one of the several layers of safety, is expected to improve safety together with

all the other procedures that we use, but is also the major source of donor deferrals, and even if we are doing medical history for the last 50 years of blood banking, we still don't know the sensitivity and specificity of the questions that we ask because we don't have the level of detail and understanding that we have about each of the assays that we use to screen our donors.

If we look at the history of hepatitis, what does it do to our deferrals? Well, the history of hepatitis, jaundice, or a positive test for Hepatitis B surface antigen or for hepatitis in general leads to deferral of .1 percent of the donors. This nationally is a very small number

Dr. Tegtmeier estimated 8,000. I estimated 13,000. I'm some that it is somewhere in between.

So the history of hepatitis is a minor contributor to donor deferral.

If we look at donor deferrals, and I hope that you can see this clearly, the history of hepatitis is in the bottom, and I have an estimate. I did a survey among America's Blood Centers. As you know, that's a community of 73 blood centers that collect about half of the blood supply in the

U.S. The total of donations for one year included in this survey is four million donations, was for 1998, and the number of donors that were deferred because of history of hepatitis in this group was 4,000. I simply adjusted it for a number of 13 million donations to get -- since I had about 30 percent in that sample, I thought that it would be a reasonably accurate measure, and so that's how I came to the 13,000.

Other things are much more important, and for instance, malaria is much more important source of deferrals. There are other deferrals. The list goes down, diminishing, and we can see it is from dental work, from Army inspection, and many other reasons.

So the total estimated deferrals that I could come with very precise data from the America's Blood Centers' registered donors of four million, these centers deferred about 13 percent of the donors or 535,000 in one year.

If we estimate what it would be for the United States, in 13 million collections we would be deferring 1.7 million donors. If we include the estimate of 2.1 percent deferrals for CJD travel, we hit the mark of two million donors deferred

among 13 million donors' draw.

I did some analysis in more detail because I had time sequences within data of the New York Blood Center, and those are annual rates of deferral. So our average of deferral, and this has been steadily increasing, and I think that there are many factors that we can potentially discuss later why the deferrals are increasing.

Yes, there is improvement in questions. There is more enforcement of CGNP. There is less flexibility on the rules, and there has been a philosophy that implanted in the technicians, the phlebotomists that work with us. In doubt, defer, and that's what is happening.

But 14 percent is our projection for this year, and the project is based on the first five months of the year, to May 31st.

If we look at first time donors, we are actively trying to recruit more donors. This federal rate is 22 percent. When we get repeat donors, those with a history of hepatitis and many other histories had already been deferred in prior donations. Even with repeat donors, we are deferring over 11 percent of these donors.

And for me this figure tells me that

there is something wrong with the system, and it may be us.

The percent, when I look at the several categories, even things that I interpreted in the past as hard data, I find a lot of variability and change. In this funny color here we have respiratory illnesses. Well, those were the winter months of 1999 that are included that, probably that influenced there, but why should the pulse and the blood pressure of New Yorkers be going up with the years? I don't know.

(Laughter.)

DR. BIANCO: While the temperature seems to be very constant, despite global warming.

We know that the ones that were the object of regulatory concern. For instance, malaria, how deferrals more than doubled over this period or four years, while other deferrals, they increased; they doubled, too, but high risk deferrals because of changes sometimes in questions and in the ways that they are done.

And we were talking about body piercing and tatoos. There was apparently an article published by AP on body piercing and interfering with donations. I did not see the exact source of

the article, but I got several reporters calling me about these data.

It's a minor deferral for us in New York. I got deferrals every year. They have increased, but I could not say that body piercing is what is having great impact in our donor base.

When we look in the donation process at the critical control points where the deferrals are occurring, they are here in blue. It is in three metaphysical and donor form questions. They are incomplete collections, technical difficulties, difficult veins or sometimes staff incompetence, and ultimately test deferrals, but test deferrals are a minor part to what happens really in the entire process, and I have a table that will show this more clearly.

That is, when we start and if we just look and maybe projected 99, we start with 500,000 donors. We defer 71,000. That is about 14 percent. We lose as incomplete 12,000, and then we come to test deferrals, 2.4 percent. Also ultimately of the 500,000 donors that registered, these are not donors that walked in and left. They completed our registration form and medical history and were entered into our computer system. I can

only recover 81 percent of those units. Nineteen percent of the units or the donors, not units, that were as part of the system were lost. And this has been decreasing over the years.

The other question that we were asking, and particularly I think this is important in light of the proposal that Becky Haley from the Red Cross made: do temporarily deferred donors give up or do they come back?

And so I asked that question more or less quickly, but based on a sample of 20,000 donors who had donated between January '96 and June '97, and then I asked if they came back sine June '97 until June '99. That is, I gave them two years to come back after the one year deferral.

Donors that had a donation reaction, 70 percent dropped out. They chickened out. History of exposure to hepatitis, we lose more or less half of them. I was very curious to know that donors that were deferred because of immunizations were only 22 percent that dropped out. Eighty percent came back, and then I realized talking to people that most of them are military donors that voluntarily under orders from the captain will show up and donate.

So as we think of our position for America's Blood Centers, we recognize the medical history questions are not always focused on deferring who should be deferred and accepting who should be accepted. That's our ultimate objective.

The questions we also recognize have been written for 100 percent sensitivity. That's what we think when we write those questions, but as if the screening test did not exist, as if they were the only thing that were there to protect is safety of the blood supply, they have a known sensitivity, a known specificity, lead to many temporary deferrals, and donors, many temporarily deferred donors do not come back.

And there are also, as I pointed out some variabilities in the metaphysical exam that must be addressed, and those are issues that blood centers must address.

We also must recognize that advances in science and technology have reduced the role of medical history and the multiple layers of safety, and that public and private resources could be applied much more productively to recruitment and of new donors and, for instance, other areas where I believe that we have not focused enough in terms

of safety is safety at the hospital level, at the transfusion service level.

So finally, medical history should be streamlined. Questions should focus on the safety of the donor and on diseases for which screening tests are not available. For instance, we know periods for HIV, HBV, HCV, and focus, for instance, on the risk behavior of the last few months because those are the dangers and should also focus on rare disease, babesiosis, malaria, Chagas, but obviously balanced to account to the very low incidence of those diseases in the United States.

And this is my last slide regarding history of hepatitis, the theme of our discussion today. Current screening tests are highly sensitive. Current history questions are nonspecific. Thus, as first step in streamlining donor medical history, we suggest that questions about history of hepatitis be eliminated because they do not contribute significantly to the safety of the blood supply.

Thank you.

DR. BISWAS: Thank you very much, Dr. Bianco.

I thought I was going to end up there,

you know. Sort of beam me up, Celso.

Our next speaker will be Dr. Toby Simon speaking for the American Blood Resources Association.

DR. SIMON: Good afternoon. I'm speaking to you as a representative of ABRA and as Chairman of their Medical Directors Committee.

I think it's important to point out that the activity of our collection centers for the source plasma industry in the United States is about of the same magnitude as the blood centers. We have over 11 million donations per year. So that represents the same number approximately of plasma phoresis donations as of whole blood donations. So we think it's important that the impact of these decisions also address the issues in our plasma industry.

We do support the efforts of the FDA to communicate with industry and all other stakeholders through a process of these workshops, and we look forward to continuing to work with you in this ongoing dialogue.

That the nation's blood supply and blood products are safer than ever before is now an old refrain, and we agree that despite this history, we

must maintain our vigilance. The source plasma industry achieves this through the many ABRA standards and programs, including a new and more sensitive viral maker rate standard for all of our donor centers.

We've also unveiled a quality assurance program designed to help plasma phoresis centers attain and implement effective quality assurance systems.

These are in addition to our other well known standards, the inventory hold, and the quality plasma program.

We do recognize that donor history screening is an area that also requires improvement over the current procedures. At best, the current screening process is long and complex. At its worst, it may be ineffective.

And what we're concerned about is that the screening procedures that we now use discourage the very type of donors we are trying to attract. We believe that busier, more well educated individuals are turned off by the long questionnaire and by the continued repeat of a large litany of questions. So attracting these kinds of individuals, we believe, will be enhanced

by reducing the donor questionnaire and making it less complex.

And so we're concerned that even as this recognition grows, the process continues to become more complex, for example, the travel question that was just mentioned.

So I guess our most important point for this discussion is that we are very much committed to taking a look at the donor screening process. We would like to see, and we believe it's important to see the elimination of outdated, confusing questions that are otherwise ineffective.

In other words, we would like to see the whole process target the questions which really impact on donor safety and allow the donor to focus on a few supported questions rather than asking a long litany of questions.

Of course, the hepatitis question, this whole workshop is a part of that process, and we support the AABB proposal to eliminate the hepatitis question.

In addition to agreeing that it does little to impact safety at this point in time, recognizing, of course, that it was probably an effective measure to reduce Hepatitis C before

testing became available, I would also like to point out from the point of view of our industry the paradox that has always existed to which Dr. Biswas briefly referred in his introduction. That is, while we ask a question to eliminate donors with a history of hepatitis, we seek the antibodies that those donors possess for the final product.

Intramuscular immune globulin is still the product of choice for post-exposure prophylaxis for Hepatitis A and was for many years the product of choice for pre-exposure prophylaxis until the vaccine came along.

So the donors that we're eliminating if we're effective with this question are donors with a history of Hepatitis A who represent no risk, but in fact have antibodies that we need for the final product.

In addition, some of the donors with Hepatitis X also represent no safety risk and also possess antibodies that are highly desirable for the intravenous immune globulin product that is used in immunosuppressed patients. We need the CMV antibodies with people who might have a history of CMV hepatitis, and we need Epstein-Barr and perhaps some of the other antibodies, as well.

So to enhance the effectiveness of the product without diminishing the safety of the product, elimination of this question would be highly desirable.

As we move on, and hopefully we can move on in this process, we would hope that we could further streamline, eliminate other questions of lesser value, and come up with some creative alternatives to the current paradigm which we could explore which would both continue the enhancement and improvement in safety, but at the same time insure that we have even more effective products.

Some of our members have begun this process in various ways. While we're trying to work with the CDC to explore research aimed at improved donor screening with regard to HIV and hope that there can be some industry initiatives to add hepatitis as well, particularly with the opportunities offered by nucleic acid testing. Some members are engaged in similar research within their own centers.

This is just the beginning. We believe that such additional research will be forthcoming and will be helpful, and that gains will help us improve the donor screening process and, in turn,

increase the quality and the safety of the products.

So hopefully we can take a step forward as a result of this workshop by eliminating a question that would appear to have little efficacy in the improvement of safety by its elimination, could improve the efficacy of product, allow us to begin to streamline, accept a few more donors who are safe.

So we think that this has been a good idea to have this workshop, and hopefully it would be the first step in the streamlining of the donor process to allow us to focus on safety during the procedure and at the same time move forward to allow us to meet the quantitative requirements for product for the American public.

Thank you.

DR. BISWAS: Thank you very much, Dr. Simon.

The next speaker represents, one, the only international speaker we could get in the short time that we knew we could get an international speaker -- we could ask for international speakers, and I'm very glad that we managed to get Dr. Patricia Hewitt from the United

Kingdom. She is the lead expert in transfusion microbiology for the London and southeast zone of the National Blood Service in the United Kingdom.

DR. HEWITT: And thank you, Dr. Biswas, and the organizers for inviting me here today. I think my children will be even more delighted as I've been able to purchase Beenie Babies not available in London.

(Laughter.)

DR. HEWITT: So it has all been worth it.

Could I have my slides, please?

I've been asked to give a U.K. perspective, and the first thing I want to say is for those of you who are not aware, there are four blood transfusion services in the U.K., one each for England, Scotland, Wales, and Northern Ireland, and I work for the English National Blood Service, but currently we are all of one, but with Scottish devolution, we may in the future find that the Scottish parliament are making decisions for themselves.

I just want to explain a bit of the background. The guidelines for the transfusion services in the U.K. are produced by a number of

standing advisory committees, which make recommendations to an executive committee which then accepts or not, and implementation is then a matter for each individual blood service.

But we are not allowed to make any recommendations which actually impact upon the cost of blood. So anything which would mean a new test or a new procedure cannot be decided on by this mechanism. That is a decision by the Minister of Health.

The standing Advisory Committee on Transfusion and Transmitted Infection has membership from a variety of sources both within and outside the blood services and include fractionators and public health laboratory scientists and has cross-representation with the standing Advisory Committee on Current Selection of Donors, and I actually sit on both those committees, which is why I had the short straw or the long straw, whichever you may thing.

Now, in the U.K., we have a big emphasis at present on what is called evidence based medicine. You will all be aware that we are currently spending something like 80 million pounds on removing white cells from blood in the lack of

any evidence that this will have any effect on transmission of CJD.

But be that as it may, we have evidence based medicine in the U.K., and I'm going to try and turn this subject on its head because we are starting from a completely different starting point in the United Kingdom. So I'm going to look at it by saying why are we concerned about a history of hepatitis or jaundice and what transfusion transmitted infections would we be preventing by excluding donors with a history of hepatitis.

Now, the causes of hepatitis have been well rehearsed this morning, and this really just summarizes what has been said all along today.

In very few circumstances would a history of hepatitis or jaundice be relevant when it comes to transfusion transmitted infection.

In U.K. blood donors, when studies have been performed, it has been shown that about ten percent of those who admit to a history of hepatitis or jaundice will have had infantile jaundice. That means within the first year of life. The majority of the remainder will have had Hepatitis A, and there will be other causes which in the U.K. would probably focus as much on

nonviral causes as with any other viral type of hepatitis, and including Gilbert's.

Now, this is an old study from 1983 from my colleague, John Barbara, and this was published many years ago when a study was done at North London where he and I are based. Eighty-eight percent of donors who gave a history of jaundice were positive for anti-Hepatitis A antibodies, compared with 16 percent of those who had no history of jaundice. So in North London donors, a history of jaundice was highly predictive for past Hepatitis A.

Interestingly, in both the west of Scotland and southeast Scotland, there was not the same large differentiation as there was in London, and I don't know the reason for that.

The other thing I should say is this is very old data. We have not done anything since then to look at whether the situation has changed, although we know that the epidemiology of Hepatitis A is changing in the U.K. in that the age is shifting and less of the population are becoming exposed at an early age and more are becoming exposed in their 20s and 30s.

We also looked at Hepatitis B markers in

donors with a history of hepatitis, and we found that 4.4 percent of donors with a history of jaundice had anti-Hepatitis B core only compared with 0.3 percent of controls.

And when we looked at total Hepatitis B markers -- that's anti-surface and anti-core -- that was in 13 percent of jaundice history donors compared with 1.6 percent of controls.

So there is no doubt that donors with a history of hepatitis are more likely than controls to have had Hepatitis B, but we also know that a large proportion of the cases of Hepatitis B are nonicteric.

We looked at a series, and again, this is way back in the early '80s, of Hepatitis B surface antigen carriers and also about the history of jaundice, and in a series of 50, none of them had a history of jaundice. But when we did find ten who had a history of jaundice, eight of them were positive for anti-Hepatitis A, and of course, it's perfectly reasonable that somebody who's reached an age to be a blood donor could well have been exposed to Hepatitis A, as well as Hepatitis B.

Now, what do we do in the U.K.? Well,

since 1975, donors with a history of jaundice have been permitted to donate, provided that they were Hepatitis B surface antigen negative because of course, that was the only test available in 1975, and that more than one year had elapsed since the illness, and that is the only criterion we have and we had until 1997 when we made one change for donors who gave a definite history of Hepatitis B.

So these are people who come along and say, "Yes, I had hepatitis, and the doctor told me it was Hepatitis B."

In that situation we will do an Hepatitis B core testing. That is not a mandatory test in the U.K. U.K. donors are not routinely tested for anti-Hepatitis B core, and this was mainly because of one case of post-transfusion hepatitis which occurred and was apparently linked to a donor who gave a positive history of Hepatitis B. The donor was surface antigen negative, but was anti-Hepatitis B core positive, and because of that one case, this change was made.

Now, we know that acute Hepatitis B occurs in the population, and we know, as has been said earlier, that the vast majority of immunocompetent adults will recover and develop

protective immunity, and having acute icteric Hepatitis B is a marker that the individual will recovery and develop immunity.

The individuals who are unlikely to recover are likely to have subclinical, nonicteric infection.

We know the majority will develop protective immunity within 12 months of infection, and we know that a small minority will become carriers or fail to develop protective immunity within 12 months.

So what we do with the donors with a history of Hepatitis B is as follows. If it is a distant history of Hepatitis B, we don't try and get confirmation of that from the donor's physician. We merely do a test for anti-core.

If the anti-core test is negative, we assume that it was not Hepatitis B, and we accept the donor. If the anti-core test is positive, we will then test for anti-surface, and we will quantitate it. Anything over 100 milli-IUs per mL is accepted as protective levels of antibody, and that donor will be accepted. Any donor who is anti-core positive and has anti-surface of less than 100 milli-IU per mL is classified as not

immune and will be withdrawn from the donor panel. So that is the only category of donor that we would not accept with a history of Hepatitis B.

We have additional guidelines for donors who develop acute Hepatitis B while on the donor panel. So these are established donors who develop acute Hepatitis B.

We will confirm that by testing, and we will monitor clearance of surface antigen. If the surface antigen is not cleared within six months, then the donor is withdrawn. If it's cleared within six months and protective immunity develops within 12 months, we will accept the donor. But if protective immunity does not develop within 12 months, then we withdraw them from the donor panel.

So in both cases provided protective immunity is present, we will accept the donor and continue to use donations.

We have recently been looking at this again in respective donors with a history of hepatitis not known to be due to Hepatitis B, and because we are concerned about these individuals, because we would accept any donor with a history of hepatitis after 12 months, we are considering an anti-core test for all donors who have had

hepatitis within the past two years. That is something new, and it hasn't yet gone through all of the stages of agreement, but we think we will be doing that for all donors who have a history of hepatitis within the last two years. We would do an anti-core test, but of course, that's irrelevant in your context as you're testing for anti-core anyway.

So for all donors who have a history of hepatitis not known to be due to Hepatitis B, we would ask if the diagnosis is confirmed by blood tests, and if so, we would usually obtain confirmation from the clinician.

Unfortunately, very many donors will tell us they had hepatitis and it was diagnosed as Hepatitis A, and they had blood tests carried out. That very often means that they had their liver function tests measured. It has been unusual until very recently for even Hepatitis A to be diagnosed serologically in the U.K. It's usually a clinical diagnosis.

But for all cases other than Hepatitis B, we would accept the donor without further testing.

I just put a reminder here about

Hepatitis C. If a donor came to us and said that he or she had been diagnosed as having Hepatitis C, we would have to consider that on a case-by-case basis, but we would be relying on our testing and not on any diagnosis that has been made in the past, possibly without the benefit of current sensitive tests. But in all cases, unless there were serological markers present now, we would be accepting the donor now.

And I'll go back to this why should this be. We know that Hepatitis A is rarely transmitted. We had a transmission threes ago, and that was from a donor who was incubating Hepatitis A. So as has been pointed out, a history of hepatitis is irrelevant for Hepatitis A transmission. It won't protect.

Hepatitis B is rarely transmitted from donors in the incubation period. We have a national collation of transfusion transmitted infection in the U.K. It's international actually because it's U.K. because that's four countries, and we know that there have been two transmissions of Hepatitis B in the last three years and both of those cases were from donors who were in the incubation period before they developed markers of

Hepatitis B and before they became clinically unwell.

So they became jaundiced after they had transmitted the Hepatitis B. So, again, a history would not have prevented those transmission.

Hepatitis C we know is transmitted from donors in the window period, and we are testing by PCR and will shortly be testing all donations.

We are testing all frozen -- well, all donations intended for frozen products in the U.K., and we've tested over one million donations now by HCV PCR testing, and we are still waiting for our first confirmed positive. So we can safely say that we have got that covered.

CMV and Epstein-Barr virus we would say are irrelevant in the context of transfusion recipients other than when we are specifically requiring CMV negative components.

GGVC, Hepatitis G, and TTV we believe is not relevant for transfusion transmitted infections, and what else do we think we would be preventing by asking for a history of hepatitis?

So in the U.K., a history of jaundice or hepatitis is not predictive of the risk of transmitting hepatitis. We do consider Hepatitis B

history worthy of investigation because we do not test for anti-core, and pragmatism reigns.

Thank you.

DR. BISWAS: Thank you very much, Dr. Hewitt.

What I suggest now is are there any questions specifically for the last five speakers.

DR. WILLIAMS: A question for Dr. Hewitt.

Of your cases who say they have Hepatitis B, how many of them actually pan out to have total core? Do patients do a good job of knowing whether they have Hepatitis B or not? That's my question.

DR. HEWITT: More recently it has been more reliable. As I said, until relatively recently patients with jaundice have not been well investigated by their own doctors because it is usually assumed to be Hepatitis A, but more recently, yes. If donors have come to us telling us they are diagnosed as having had Hepatitis B, it's more likely to be reliable now, but if it's a diagnosis that was made some years ago, we would be very suspicious.

So we would usually just do a core test

ourselves rather than try and get any confirmation of the history.

DR. BISWAS: Okay. I think what we'll do now is have our break and caught up, and at 2:40 we'll gather here again for the panel discussion.

(Whereupon, the foregoing matter went off the record at 2:20 p.m. and went back on the record at 2:39 p.m.)

DR. BISWAS: If I could please ask the speakers to come up here. It seems like half of the audience has come up here. Is this working?

Okay. Well, to start things off, firstly I would request that everybody speak into a microphone. So if members of the audience have questions or comments, please use the microphone. We did lose some of what people said this morning.

The second thing I'd like to say is that some members of the panel have indicated that they'll have to leave a bit early for planes and cars and things, and we will stop around about, oh, 20 minutes to four at the latest, but if we all run out of breath, then we'll just finish.

I believe that Dr. Tabor would like to make a comment.

DR. TABOR: Well, it's sort of almost a

rule of thumb that once you have a regulation, it's very difficult to get rid of it, and this is a very good example of that. We've dealt with this regulation over and over again.

In my presentation this morning, I described an effort to come to grips with it in the '70s when the sensitive assays for Hepatitis B were first available. FDA tried to deal with the issue of possibly removing this regulation or altering it in the 1980s.

I did not mention that it was the subject of an international forum in Vox Sanguinis in 1981. Some of the people in the audience here probably were contributors to that.

The second point I'd like to make is that we've heard a lot of really interesting data today. The problem is that most of the data, not all of it, but most of it deals with what donors with serologic markers can be picked up by asking them if they've had a history of clinical hepatitis, and that's not the issue here.

The issue is what donors without serologic markers can be picked up by asking them if they have a history of clinical hepatitis, and it may be that in the discussion of the panel we'll

have to address ways in which we can get the answer to that question.

DR. BISWAS: Well, I think the way to start off is to say that this history of hepatitis question has been controversial for the last two decades almost. Is there any reason to modify it, any reason to eliminate it, any reason not to eliminate it?

And alluding to what Ed just said, would one miss anyone with hepatitis, with viral hepatitis, if one did not ask the question?

So would anybody like to start off?

Harvey.

DR. ALTER: This is my feeble attempt to answer that question. The way I look at this is that we're talking about is there a history of hepatitis. So if that initial hepatitis was due to HAV, the history has no relevance because there is no carrier state. So we can forget about HAV.

If it was HBV, it would at best have minimal relevance because 90 to 98 percent of people with Hepatitis B recover because you have very good markers to detect carriers, at least two good markers. Maybe we'll add genomic testing.

Now, there is the issue of sero-silent

HBV carriers, and there are variable estimates of whether they -- of their numbers, but they're probably rare, and their infectivity is unknown, and I think they cannot be very infectious because we just don't see Hepatitis B post-transfusion for a long, long time.

The Japanese have followed this very carefully, and it has virtually disappeared, and they had a lot before.

So it gets down to HCV and non-A/B/C. For HCV, we know the history is not very meaningful or at least no more than 25 percent have a history of hepatitis. We have excellent serologic markers. We know the window risk now is one in 100,000 to one in 200,000, and that in our prospective studies we haven't seen any further HCV since 1992.

And we know that GAT testing, I think, will totally eliminate the HCV risk. So I think HCV, the history issue is to relevant to C either.

So it gets down to non-A/B/C, and we know here that the vast majority, if not perhaps all of these, do not have a history of an overt illness. I'll show you a little bit of the data that we have.

We don't know the rate or the severity

of the chronic hepatitis. I'll show you, again, a little bit of data, and since it's probably, and we have a little bit of data of this also, that these people co-associate with HCV, and they have similar risk factors, that probably the questions we ask, the HCV serology we do will eliminate a significant proportion of these cases.

So looking at these 13 cases of non-A to E hepatitis that we have from the transfusion setting, looking at the clinical parameters, we found that none of these cases were enteric; that the ALT levels were generally low. Although the range was 135 to 1,740, the median was only 200. The mean ALT was 373 for the whole group, but if you take out that one patient with a 1740, the mean was 259. So almost all but two of these cases had ALT levels less than 300 or 350.

There were, however, four of these patients that had intermittent or persistent ALT elevations for as long as we followed them, which was greater than one year. So it's possible that there is a chronic carrier rate that might be around 30 percent from our limited study. However, these were not -- we're not measuring viremia over time. We're just measuring ALT, and that could be

due to other things.

So the way I put it together, I had found a paper which suggested that the risk of a history of hepatitis or a finding of a history of hepatitis is about .1 percent and Celso's data has confirmed that. So if we looked at a million donors, there would be 1,000 who gave a history of hepatitis.

Based on the CDC data that three percent of overt hepatitis is non-A/B/C, then out of that group 30 of the 1,000 would have had non-A to E hepatitis. Based on our data that there might be a 30 percent change of chronic hepatitis, then there might be nine carriers out of the 1,000 donors who gave a history of hepatitis, and that would be .009 percent of the original million.

Now, if we assume, and this clearly is an assumption, that the current screening measures, serologic and questioning, would exclude 50 percent of these, then we would have 4.5 eligible donors out of that 1,000. If there's a 90 percent transmission rate, and this is unknown, but that's what it's been for the other viruses, there would be four infected recipients from these 1,000 donors. The risk of overt hepatitis, .12

recipients or 0000012 percent of the original million would have overt hepatitis, and it would be one recipient who might develop chronic hepatitis based on the 30 percent figure.

So we would exclude 1,000 donors to theoretically prevent one case of clinically significant hepatitis, and this is a minimal estimate because it may be that none of these donors would have a history of hepatitis, none of these carriers would have a history of hepatitis.

So I don't think this is a very good payoff, and I think it's time to have some guts and get rid of a question which has very little clinical relevance. This is in the range of the value of ALT or some of the other things we've dropped out.

I think if we don't start looking at these questions, it'll leave us open to asking ridiculous questions, you know, like -- I can't think of a good example, but maybe we'd ask a question like have you eaten meat in England, something silly like that.

Yes, Celso.

DR. BIANCO: Harvey, what is the basis for the assumption that this case, one in 1,000,

would be picked up by a history question?

DR. ALTER: No, I'm saying there is no -- I just have made these estimates all along the way, and in point of fact, none of our patients, but it's only 13, had a history of hepatitis, but there are some people who have come into the CDC who do have a history. I mean they have what looks like non-A, to be overt hepatitis.

So somebody must have a history.

DR. BIANCO: And that, I would ask you, the clinician and the epidemiologist, what proportion of those cases that would be missed would be contained in this. It's not a common occurred.

DR. ALTER: No, it's a rare occurrence. I think these numbers address that, that if out of the four -- let's see. Well, I don't know. I mean I've used the CDC three percent number and my 30 percent number to come at these estimates that there would be one case maximum of chronic hepatitis. It could clearly be less.

DR. DI BISCEGLIE: I mean, one way to think out obvious data is to say we don't know a number, but what's the worst case scenario and what's the best case scenario, and I think what

Harvey is trying to do is show the best case scenario, whichever way it is, the one extreme, that they're the confidence intervals is what you're talking about.

DR. ALTER: Right.

DR. DI BISCEGLIE: And this would be one extreme, and the other extreme would be you wouldn't find anybody.

DR. ALTER: Zero, yeah. So it's between zero and one case out of a million.

DR. KOFF: Harvey, can you bring us up to date? Have you transmitted this form of whatever it is to animal, a chimp?

DR. ALTER: No.

DR. KOFF: Is this a transmissible agent? Do we know that yet?

DR. ALTER: We know that -- not exactly.

(Laughter.)

DR. ALTER: We know that it's transfusion related. In other words, people who get transfused get it at a -- who get transfused and get hepatitis get it at a reasonably high rate. People who are transfused and don't get hepatitis have it at a much lower rate, and people who are not transfused have it at a much, much lower rate.

So whether it'll transmit to a chimp I don't know, but I think it is transmissible, but you know, I apologize for the press release. It's to early to say a lot of things.

DR. BIANCO: There is one experiment that has been done that is not asking the question. Maybe Patricia wants to tell us how many cases of hepatitis per transfusion you detect in your SHOT reporting.

DR. HEWITT: Thank you.

The SHOT reporting system -- that's the serious hazards of transfusion -- has only been official for the last two years, but in those two years, there has been one transmission of Hepatitis B and one of Hepatitis C actually proven to be due to transfusion.

And there was another report of Hepatitis B, but that was a case that occurred five years ago. So that was a very late report.

The Hepatitis B was from a donor who subsequently became unwell with acute Hepatitis B, and the Hepatitis C was a window period donation.

There are 2.5 million donations a year in the U.K.

DR. KLEINMAN: I would like to suggest

that maybe we should -- you know, Dr. Tabor put a question on the table in a certain format, but I think that it's worth reformulating that question, and I think that's what Harvey has done, reformulated it to what is the expected value of continuing the question rather than can we prove that if we take the question away we won't ever have another case of hepatitis that we could have otherwise transmitted.

If we formulate it that way, you know, I don't think that proof could be obtained. I mean the only way, you would have to take the question away and see what happened, and you'd have to have reporting systems that were good enough to be able to monitor it or you'd have to do a controlled study, and I don't think it's likely that either one of those two things are going to be done.

I guess the best information would be from the U.K. where they're not asking this question about lifetime history, just one year history, and there they're -- at least their two documented cases would not have been prevented, I assume, by any kind of history question.

So it seems to me that we can't ever prove a negative when this is a problem we get into

with deciding whether we still have to do RPR testing, and that was the whole discussion at the consensus conference. Well, we haven't really proven it. We don't think that removing RPR testing would be a problem, but there is no data. Now people are beginning to do PCRs and that sort of thing.

So I think if we can prove with the data that we have that the existing risks are vanishingly small and that we know we have a very nonspecific method and nonsensitive method to deal with those risks, that maybe that ought to be good enough to take an action. Just another way of thinking about it.

DR. TABOR: What you say is all correct, but you know, we live in a world where we're doing P24 antigen testing for HIV to detect on case in millions and millions and millions of donations since the test went into effect. A few decades ago it would have been unacceptable to eliminate 1,000 donors to prevent one case.

Today I think we live in a country where it might be very hard to eliminate a regulation under those circumstances, but the other point you made is also very good, and that is that the U.K.

is really doing the experiment for us, and the question is: how long do we have to wait until we have enough data?

Does anyone have an opinion?

DR. HALEY: I have an accidental experiment of sorts from the American Red Cross where people remembered later that they happened to have hepatitis, and they say, "Oh, I was talking with my mom, and she said I was really 12 and not ten when I had hepatitis," or, "oh, I forgot about the time when I turned yellow."

And we have 273 cases that we pulled up before this conference, just before this conference, an average of about ten components per donor that we've withdrawn, and we've not had a report, and all of these were positive history of hepatitis, but we've had no reports of hepatitis from that.

So we've have the accidental experiment in no way controlled that has allowed us to examine some of those cases, and I think we have 107 going so far this year, 273 last year, 107 this year, and we haven't seen any hepatitis in those.

So it's not a controlled experiment in any way, but that's what we've seen.

DR. BISWAS: Harvey, you had something?

DR. ALTER: You make a very good point. We should stop doing P24 antigen testing.

(Laughter.)

DR. EPSTEIN: From the FDA point of view, I don't think that we have to regard ourselves as locked in by past policies. It's only that we have to be very public and make decisions based on sound science in order to change those policies because presumably they had some preventive value or were thought to at the time, and we just want to be sure, and we need to be sure enough that we can also be convincing to the public and health professionals.

So I think a little bit it's a strawman argument to say that the environment doesn't let us change. I don't believe that. I just think that it's a question of a process which is judicious and public.

And let me say further I do believe that given the accumulated policies dating back several decades that it is timely that we should reexamine both our testing and our history based donor suitability deferrals because we do recognize that scientific technologies have changed, as well as

public expectations, but that some of the things that made sense in the past may not make sense now.

So I at least have an open mind on that. I think our concern though is that we should have a proper process.

On the question at hand though, I like the way Dr. Alter approached the problem, distinguishing the risks related to known agents versus the risks related to unknown agent. I think that it's a very different analysis in those two cases, and that we kind of have to keep them separate.

I'm impressed. I think that the risk from known agents really has to do with mainly how concerned we are about the so-called sero-silent Hepatitis Bs that have been reported. That's really the main thing that I've heard where we kind of have to be careful.

The risk from unknown agents, so-called Hepatitis X or cryptogenic hepatitis, I've heard enough to convince me that there probably are agents of such hepatitis, and I think that what we're suffering from is at this stage of knowledge some incompleteness in the data. We don't know what the full range of disease potential is. We

don't know what the frequency of event is. We don't know.

You know we have projections from small numbers what percent may be chronic. The only thing we really do know is that it probably exists and it's a non-zero risk.

So I think the main challenge there is quantitation of risk so that we can be rational about what we do.

I think the issue of the history of hepatitis is whether it's discriminatory with respect to hepatitis risk. Now, what I've heard about prior infections by known agents is that it's actually pretty good. I mean we keep hearing it's nonspecific, but I heard data that suggested it wasn't nonspecific; that if you look back at people who have a history of hepatitis, the likelihood of finding a positive marker for Hepatitis A, Hepatitis B, or Hepatitis C is very high.

So I don't think we should keep saying it's nonspecific. I think we should feel good that it probably had some meaningful utility to prevent Hepatitis C before we had hepatitis screening, and I think that what we really need to ask is whether for the known agents it's helpful to prevent

residual risks.

And I think a case can be made that any residual risks in the face of the history are remote.

With respect to the unknown agents, I think the only piece of data that I heard today was from Dr. Tegtmeier, and admittedly it's soft data, but that there is a correlation at least in the studies available with persistent elevated ALT, and to me that's a red flag.

I mean I don't know where you go with that piece of information at the epidemiologic level because of all the points that Steve Kleinman made, that you don't have a proper control in this study.

But still from what we heard there is a correlation with elevated ALT. So there's something to worry about. That's the way I look at it.

And I think that Steve Kleinman also made a very important point, which is that one of the problems that we face is that if we have a precautionary measure in place and we don't know its contribution to safety, we have a dilemma because we can't study that without removing it,

and than that gets you into a circular logic because you want to be sure you can remove it before you remove it, but you're not sure you can until you remove it. So you're stuck on that circle.

Well, the question that I would put before the group is would studies in an animal model, and I presume it would be a chimpanzee, be useful because it's easy to envision that we could readily collect blood from prospective donors with and without history of hepatitis and eliminate the units where we have testable markers and then put the remaining units in the two groups presumably in the form of pools or pellets made from pools into chimpanzees and directly ask the question whether the history is discriminatory.

Now, you might get one of three outcomes. The pools made with and without the history might not transmit the chimpanzees. We might not know that the agent is one to which chimpanzees are susceptible and we wouldn't learn anything.

On the other hand, we might get infection from pools associated with history and not from pools not associated, and then we'd be

arguing over the numbers. In other words, are the statistics strong enough that it meant anything? You know, because it depends how large the pools were.

On the other hand, you might get infection in both groups, which I actually think is the likely outcome, but then you would probably conclude that at least for the frequencies reflected in the pools, the history question is not discriminatory. So it may not be irrelevant, but it's not useful.

So I think that the question really is are we willing to do the experiment in man, and I accept the point that there is useful comparison with the U.K. and possibly other countries, or do we first do it in chimps? Because what I think I've heard is that there probably is Hepatitis X. We don't know the full disease potential, and there may be a correlation with history of hepatitis.

And so the question is: do we simply take our crude estimates and say that's good enough, the risk estimates, or do we test it somehow first? That's my take.

DR. FEINSTONE: Let me just say a few things maybe not because I have so much to say, but

because Robin asked me to join the panel, and I figured I should say something for the free lunch.

Specifically in response to what Jay said about the chimpanzee experimentation, there have been a lot of non-A through E samples, human plasma samples or serum samples injected into chimpanzees without much in the way of a result. Whether or not this recent finding of a new virus, SEN-V, I think it's called, reported yesterday in The New York Times will give us some specific markers for chimpanzee experimentation I think remains to be seen, but just to go off and blindly do more chimpanzee experimentation without any specific way of analyzing the chimps other than the presence or absence of ALT elevations at this point I think is not going to be very useful.

One point I did want to make is I remember Jay Huffnagle once said to me that an anti-core test is basically a marker for intravenous drug use. I think that in many ways Hepatitis C from what we've heard today is also largely associated with illicit use of intravenous drugs.

Hepatitis C remains not a perfectly well defined disease as far as the natural history of

the disease and the immune response to the disease. If we look in the chimpanzee model, for instance, where we have very good serial data we've seen chimpanzees that are infected with Hepatitis C, that clear their infection, and that never develop detectable antibody to Hepatitis C.

Now, if we have patients also in that category, we know that patients who have developed Hepatitis C clear their infections, often lose their antibody over time, but are those patients still in that same high risk group that got them their Hepatitis C in the first place? I think that's just one small concern.

I think that overall though I feel that most of the information presented today is compelling about the value of the history of hepatitis question.

I should just say one thing about Hepatitis A. With as much affection as I have for that virus, I am really in full agreement that this is an irrelevant problem for blood transfusion, but not only do I feel that it's irrelevant for blood transfusion. I've also argued strongly that this is an irrelevant problem for plasma products as well.

I think that anyone who is receiving plasma products on a routine basis needs to be vaccinated against Hepatitis A. The vaccines are superb. They will protect, and that's what vaccines are for.

I don't think that we need to invest incredible amounts of money trying to learn how to eliminate Hepatitis A that may very rarely contaminate plasma pools.

DR. TABOR: Can I ask? Steve, when you said you thought the data was compelling -- I think that was the word you said -- could you just clarify and make sure I understand in which direction it was compelling?

DR. FEINSTONE: From what I heard today and probably also my basic prejudice is that asking the question of the history of hepatitis is not of significant value in eliminating the transmission of hepatitis, with this one caveat of Hepatitis C as placing somebody in a high risk category for the nonidentifiable hepatitis agents that certainly exist.

Now, hopefully this recent finding -- I think the data that Harvey has in which this group that has developed an assay for this agent has been

able to generally break a coded panel is very exciting, and once we have, if we have, another specific assay that will then further eliminate the very small amount of residual post-transfusion hepatitis, then I think it becomes even more compelling that this question is not very useful.

Even with the situation today, it certainly look like it does not eliminate hepatitis.

DR. ALTER: Well, Jay, I thought that that was, as usual, a brilliant summary of what the issues are, and even though I feel that the question has a little relevance, I think you raise very valid points.

I agree with Steve that that particular chimp experiment probably is not going to pay off, but it is clear, and I didn't want to talk about this agent because I still think it's too premature to talk about it, but if it turns out to be real and we can show viremia levels, then we can transmit, try to transmit at the time of high viremia, because I remember in non-A/non-B people tried to transmit the chimps for years and years and years, and it didn't work, and then suddenly just by picking out the right samples at the right

time, everybody could transmit it at that point.

So the fact that it hasn't been transmitted yet doesn't rule it out, but if there is, indeed, a chimp transmissible agent or this agent proves to be real -- let's put it that way -- one way or another, then you could apply this test to donors who have a history of hepatitis and donors who don't have a history of hepatitis. So I'd go that direction, although there could be more than one agent.

I'm sorry. Just one more point.

However, if this proves to be real, the issue then is not going to be whether we should get rid of the history. It's whether we should add a new test, and that's going to be the next panel here.

DR. BIANCO: Well, that's more or less the point. Those 12 pairs that you have there, they all said no to the history of hepatitis question. They were asked the question. So -- well, the donors, but those are the ones that I think we're talking about.

The cryptogenic hepatitis, would any of those cases have been presented by medical history questions? If they could transmit disease and if

they walked in to donate, would they have a history of hepatitis?

I don't think they would really, and so I think that we have to go back a little bit to the beginning and ask how many of those SEN or strange viruses or TTs and Gs and whatever would be prevented by a question on the history of hepatitis.

DR. ALTER: Yeah. It's somewhere between zero and zero plus one.

DR. FEINSTONE: Did you have any donor recipient pairs in that coded panel that you can tell us?

(No response.)

DR. TEGTMEIER: Harvey, a question for you. The current post-transfusion hepatitis study that you're orchestrating in the greater D.C. area, what's the denominator there now and the numerator?

DR. ALTER: The study is ended. We're starting a new one. So the final denominator was 651 recipients with zero C and one non-A to E. No cases since 1992, but there was one just before that.

PARTICIPANT: (Inaudible.)

DR. ALTER: No, he got over it.

PARTICIPANT: (Inaudible.)

DR. BISWAS: Gary, can you turn your mic?

DR. TEGTMEIER: The hepatitis X patients from the CDC study, what percent of them became chronic? Was it 30 percent?

DR. WILLIAMS: I think it was in that ball park.

DR. TEGTMEIER: Okay.

DR. WILLIAMS: One other point that sort of segues into Harvey's point is should you remove this question, the ability to assess its impact on increased risk. You would be unable to assess its impact.

I mean I think Harvey said he hasn't seen a case of Hepatitis C transmitted since '92. We haven't seen a case transmitted since '94. It doesn't mean Hepatitis C hasn't been transmitted. It's just we don't have a sufficient surveillance system to capture those things.

So I think at issue here is the risk is small. If you should remove this question, then the risk should go up and we're never going to be able to assess it. We're never likely to be able to assess it.

DR. BIANCO: Or if it comes down.

DR. ALTER: Or if it goes down for that matter.

DR. TEGTMEIER: I think one other thing we're lacking is data on contemporary donors with a history, and I think it perhaps is something we should collectively undertake to accession samples from such donors and have a central lab test and ascertain what marker rates of known agents are found.

All of the data we talked about is 15 to 20 years ago.

DR. HALEY: Once again, since we don't accept those donors, we don't know what the marker rate is. We would have to go on a project to do that.

We have our accidental group here of about 400 which no markers and no subsequent disease and, again, about ten components a piece, but that was in no way controlled.

DR. TABOR: Clearly because these donors are not accepted at an early stage in the process and they're excluded in a early stage in the process, it would have to be done under an organized, funded study, and if this panel feels

that there's a reason to try to do such a study, we can bring it up at various FDA, NIH, CDC joint conferences to see what funds can be channeled towards such a study.

DR. BIANCO: I would love to see that study done.

DR. HALEY: We would love to see the study done. Besides I wouldn't have to sign so many letters of apology for people, for contemning them to another category of human because they can't give blood.

DR. BISWAS: Jay?

DR. EPSTEIN: Well, I guess I see the issue a little bit differently based on the numbers. If we're deferring .1 percent of donors, where's the urgency? You know, we have bigger concerns right now. I think it's important. I think any and all unnecessary deferrals should be eliminated. I think we have to, you know, adhere to current good science.

But, on the other hand, there's the issue of the timing, and if a new agent has been discovered, if that's going to enable us to really find out what's true both about prevalence, transmission, and the value of the question, then

why rush now?

We're paying a small price for what may be a very limited precautionary measure, but we have the opportunity maybe to learn more in a short time. So I kind of see it the other way around. I see the .1 percent as, you know, lowering the --

DR. TABOR: Well, the only thing I'd like to point out about this so-called SEN-V virus is that we had very similar articles in The New York Times when TT virus came out about a year and a half ago, and then HGV before that. So it seems as if every 18 to 24 months we have a promising new virus, and I think that's good. It shows the people are doing research and are, you know, looking in the right places. They just haven't found the right agents yet.

Even if this does turn out to be an important virus, and I think the most compelling thing in its favor is that Harvey Alter is involved in it. If it were just coming from the company without that sort of academic involvement, I think people would be even more skeptical.

But even if it does turn out to be correct, look at the time lag from when HCV was transmitted to chimpanzees or even from when it was

cloned until the time when we really had answers about screening tests and prevalence and so forth.

PARTICIPANT: (Inaudible.)

DR. TABOR: Well, it depends on when you start counting from. You're right. It could be one year, but it's certainly at least a year, and it could be longer if you count from an earlier event.

I mean Chiron gave a press conference with some of that data, but a large part of the community was not privy to the data or the tests until yet another year had passed.

DR. HAMILTON: Excuse me. Could I?

My name is Jan Hamilton. I'm a Medical Director for the Plasma Centers connected with NOBI.

And I would like to point out that while I don't have an exact figure, the number of donors that we turn down is far in excess of 0.1 percent. We are turning down donors who have been exposed to someone who has Hepatitis A. We are turning down donors who have tried to donate blood and tested positive for Hepatitis B core antibody, but they can't tell us what test, and we have a question, "Have you ever been turned down for

donating blood or plasma?" and they answer yes, and it's because of a test that was done of questionable validity, and then they come to us, and then we turn them down because they've been turned down for a test that we don't even know what they've had.

We also end up turning down people who don't understand what test they had. When we ask about hepatitis and they say yes, it's over. We can't rely on the fact that they way, "Well, I had Hepatitis A when I was traveling in Spain," or, "I had a test before I had a Hepatitis B immunization to see if I was eligible."

We often do not have the full information, and yet the very word "hepatitis" automatically excludes people from our donor pool and excludes people whose immunoglobulins are very valuable to the patient population who receives them.

So I don't think we're talking a small number. I wish Toby Simon were still here to address the numbers. Oh, you're on the panel.

I just think that we had this conference because it is an important question. If it's not important to the whole blood industry, it is

important to the plasma industry.

DR. HALEY: I'd like to point out that although we had 4,300 deferrals in 18 months for the hepatitis question when we had about nine million donations, only about a fifth of those were subject to that kind of deferral because four fifths of those were repeat donors who have already been selected out for that question before.

So I would like to suggest that perhaps the numbers are not absolutely what they seem because most of our donors are repeat donors. Only a small minority are first time.

DR. SIMON: We do have the accumulative effect, but I guess where I was going from Jay's point about if it's a small enough problem why would we deal with it, and it seems to me that it would be ideal if we could grasp the bigger problems, but if we do need to move in a step-wise direction and based on scientific evidence, this would seem to be a good place to start.

Clearly, I think the shortages of blood and plasma are acute enough that any positive step is a useful one. I think one step based on the evidence then could lead to other steps and we could progressively move through and improve the

donor questionnaire and eliminate the less important questions and then focus on the important ones.

DR. KLEINMAN: I think the panel is focused on the issue can we eliminate the question, and that was what several of us were suggesting, but there were other suggestions, too, which is that the question be modified either to include a one year deferral. That was one suggestion.

I suppose another suggestion that could be made is that if there's a history of Hepatitis A at whatever age, could we accept that donor, and if so, then what kind of documentation would we need? Maybe just a donor's history might be good enough.

I think once you get into having to pull up the records, forget about it. I mean, it's not worth it. You can't do it. But why is that necessary when the risks are so low?

Somebody says, "I give you a history. Yes, I had hepatitis when I was 15, and my doctor told me it was Hepatitis A." Why shouldn't we believe that? We see the charts that Hepatitis A is a hell of a lot more frequent than Hepatitis B or C at every age. So why would a person make that up?

So I think we could make some modifications short of getting rid of the question that still, you know, will fulfill the basic tenets of protecting recipient safety, increasing the number of donors and hopefully making more scientifically valid use of the medical history.

So I really hope that if the FDA feels that there is not sufficient data to drop the question, then I hope they don't drop the issue because I think there are some other ways that the question can be modified.

DR. ALTER: Yeah, in my comments that we don't need the question, I think it was implicit there would be a question about have you had hepatitis in the last year. So we would cover the seroconversion period.

But that could be built into our existing questions rather than being a separate question. So I think if we drop it, we should do that.

I think another comment is that if it's 8,000 donors we're losing in a whole blood sector, it's 8,000 donors, but that's 12,000 to 16,000 donations, and it's 36,00 to 48,000 products that are being lost. So that the numbers increase as to

the magnitude of this loss.

And lastly I think, you know, two things are going to happen. Either this new virus will pan out, in which case we could then reevaluate this thing, and it'll still have the same question because then it will be is there a non-A and non-whatever, and if it doesn't pan out we're where we are today.

So I think for this panel to be meaningful, we ought to try to think let's forget about the new virus. What would we do just on the evidence presented here? Is it valid to keep that question?

And nothing is going to happen. You know, it's not going to happen for -- even if we decided to change it today, it won't happen for a long time. So that by that time there will be more information.

DR. BISWAS: Harvey, could you just repeat? Maybe you already said it, but could you elucidate how important, if it does pan out, this new virus; how important would it be number-wise?

DR. ALTER: I don't know how much non-A to E is being transmitted right now. It seems to be very small. It seems in our hands, in our small

numbers, to have sort of disappeared along with C, and the only reason I could think of that is because there's some co-association with C and because we asked such difficult questions already, not history, but all the other things we asked, and there's less blood being used.

But anyway, I don't know. You need a new, large, prospective study to see what the current rate of this entity is.

DR. BISWAS: Okay. Thanks.

Blaine.

DR. HOLLINGER: I think both Harvey and I would probably have similar questions about the numbers in terms of the donors.

Harvey, you had 13, I think you said. What was the denominator again on those number of cases? You had 13 cases out of what, 1,000?

DR. ALTER: Oh, no. Well, 13 is our cumulative experience out of, oh, roughly 108 or 12 cases of combined C, CMV and non-A to E.

DR. HOLLINGER: But of the total recipients?

DR. ALTER: Oh, well, these I can't give you that. Since 1990, we've had one case out of 651 recipients. The total recipients over the

years is about maybe 3,000, the 13 out of 3,000, something like that.

Well, the reason I was asking, again, the TTV study we saw the same kind of thing, a group of non-A/non-B/non-C hepatitis cases, some of which became chronic, and, again, the big problem is that obviously these were donors who had been asked the question where they had had hepatitis in the past, and those who had given a positive answer were excluded.

So what we know is this is what the baseline is in this population with donors who had answered no. What we don't know and probably may not get the information, but what we don't know is what the risk is. If the donors who had answered yes on the question were allowed to donate would we have a lot more cases?

I think Gary had some excellent data on their study back in the '80s which showed that there was some specificity to the question of donor history in terms of BNC, and so the same issue would be here. Maybe we have perhaps its a tenth or one percent cases of non-A to E cases that are occurring. Would it be higher if the current donors who are answering the question yes were

continuing to donate?

Maybe what we should do is sort of what the Chinese do. As I understand, at the millennium they're going to make all of their CEOs of the airlines fly their own planes between December 30th and January 2nd to make sure that they don't have any Y2K problems. Maybe we should do the same thing with the question: those who are in favor of eliminating the question of donor history, we should provide them with blood from those donors to see whether or not they would get hepatitis. It would be one way of doing it.

DR. ALTER: Blaine, that's sort of the argument that's been used for maintaining syphilis testing. Yeah, we can't show it does anything because the rates are so low, but the rates are probably so low because we're doing the testing. You can't get out of the conundrum.

The other way to look at it is we've been asking this question forever, okay, and the rates keep coming down as we add new measures, direct markers, surrogate markers, and the rates have been coming down and coming down, and Hepatitis C was the next big thing that really brought it down.

So although the question has been level, the rates have dropped. So that's not a direct assessment. It seems to me that the question no longer has much relevance to the rates.

DR. KLEINMAN: Sorry, Harvey. I wanted to just comment on one other thing and expand on that. It seems to me that the data that we saw from Kansas City, as an example, where most of the, if I recall it correctly -- was it most of the donors, Gary, with a history of hepatitis had some marker?

DR. TEGTMEIER: Two thirds.

DR. KLEINMAN: Okay. So I mean, you can look at that two ways. On the one hand, you can say that that was a useful question in the past, which it clearly was preventing C, but the flip side of that is that most of the people with a history of hepatitis are accounted for by known agents, A, B, and C.

So that if we're saying the reason the question is still in place is for an unknown agent, at the maximum most people who give a history of hepatitis who give that history will not have the unknown agent because we already know they have A, B or C in the past.

And so -- unless they have both, which, I mean, I think is certainly possible, but not that likely -- so I think that, you know, we can define the level of utility that we might find, and it has to be much smaller than the universe of people we're deferring.

So it's a very indirect way of looking at it, but I think it supports the fact that if we're doing anything, we're probably not doing a whole lot, and I guess, you know, my sense is that there's a consensus with the statement I just made. If the question is doing anything, it probably isn't preventing a whole lot of post-transfusion hepatitis, but the issue is is it preventing any, and since we can't prove that it's not preventing any, that makes people want to be cautious as to what to do next.

So, you know, I'm just restating, I think, what we've already discussed, but maybe we can find some ways if we don't eliminate the question to say, "Okay. Part of what we're doing is eliminating people with a history of Hepatitis A and we all agree that there's no reason why we have to eliminate people with a history of Hepatitis A."

I can tell you the question that comes

up, and I'm sure FDA has heard it many times either at meetings or from donors who eventually get to them, is if I had hepatitis before age 11 and you're willing to infer it was Hepatitis A, how come when I come in and I have hepatitis at age 20 and I tell you it was Hepatitis A because that's what my doctor told me you won't take my blood?

That makes no sense to the person who's being affected or to the medical director who has to explain it to that person. So maybe some change along those lines could be made.

DR. HALEY: I would like to throw infectious mononucleosis, EBV, and CMV in there also. It makes no sense.

DR. BIANCO: If I can, I think that we can't lose the perspective. We are focusing back, I think, in the main question of the workshop, that is, the history of hepatitis, but each one of the many questions that we're asking influences or interferes with the other one. Is it time? Is the tiredness of the donor? Is lack of attention? That is, a donor will pay much more attention to the history of hepatitis than about a history of drug use.

And so I think that we have to try to

streamline the questionnaire, and we have to start somewhere so that we focus on the things that we know are important in big ways, not in the things that are potentially important in small ways because of a rare virus published in The New York Times.

DR. BISWAS: Well, it seems as though we've talked ourselves out. Any last remarks for the last two or three minutes?

DR. BIANCO: It was a very good day.

DR. BISWAS: Well, thank you very much.

Well, I think you've given us -- this scintillating panel here has given us a lot to think about, possibly a new Hepatitis A to chew on, possibly some sort of experiments about it, chimpanzee experiments or something, possibly modifying the question, but no doubt, we will go back to our work places and discuss this further and think what our next steps should be to handle this question.

I thank all the speakers very much indeed for their active participation and members of the audience as well. It's been really a very, very interesting and thrilling day certainly for me

Thank you.

(Whereupon, at 3:35 p.m., the workshop was concluded.)