come back, and all of the subsequent donations are negative. And then we also have the category where we have multiple NAT positives in subsequent units.

So we have a total, a total of 42 donors positive. This is just the number of the positives. This is the number that entered the clinical study, that accepted our invitation, and this is the number that met the definition of seroconversion while they were in the study. So we have 13 of the 15 who entered the study who seroconverted.

This is a graph of all 10 of the positive HBsAg, the subsequent positive HBsAg donors, and you can see that by the red triangle, and this charts their donation history. You notice we have some that never came back; some that gave multiple donations that were PCR positive but then became negative. And this is a pattern that we have seen, we have seen normally, I guess we could say now. We didn't understand it in the beginning. We probably still don't understand it.

What we also did is, we calculated the time between the first PCR positive and the last serology negative donation, and that was 10 days in this group of five donors. Remember we talked about the multiple positive donors on the previous slide. Those eight donors remained positive for an average of 11 days. Okay?

Now, one of the questions we have been asked was,

what does it look like when you find the PCR positive? What is the antibody, the neutralizing antibody characterization? So we first started obtaining information based upon the anti-HBs, and then we decided we need to look also at the anti-core, since we don't do that as a normal test. What are we finding at the time--this is a snapshot--at the time of the NAT positive? And we find the majority of our donors do not have high antibody to HBs. We have some, we have 3 that do, 19 that do not.

Now we also wanted to characterize this again into how many of these entered the clinical study, and from each of these categories, how many actually seroconverted? And you can see that we have a large majority, both anti-HBs and anti-core, who entered the clinical study and also seroconverted. We had some with no additional data, and we did not consider the HBsAg positives in this analysis.

Well, here is my one research slide. These are panels that we tested for hepatitis B, and if you remember when I spoke about the multiple positives, approximately 11 days positive, when we had the 10 donors, we looked at the 10 donors that were HBsAg positive and we found that the time from the first PCR signal to the last serology negative result was 10 days. That is in the pool system. Looking at this, we see that you are basically looking at anywhere from 14 to 20 days with the PCR signal being positive before the

HBsAg.

So what does this mean to us? As far as from the plasma point of view, we have 32 donors out of the 42 that did not have a subsequent HBsAg reactive unit, so these donors would not have been identified by the normal serology look-back notification. They also donated approximately 300 units. Thirteen of these 32--we are going to forget about the 10 serology positive donors, we are going to concentrate on only this grouping--13 donors entered the clinical study from this category. The other two entered, they were HBsAg positive. And we find, of the 13 that entered, 11 seroconverted. Eleven developed antibody to core, eight with IgM. Only one became HBsAg reactive in the clinical study; the rest did not.

This is a time graph of one of these donors. This donor donated multiple times for the first seven months of 1999. All of a sudden we got a PCR positive in July. A couple of negative units, then two more positive units. This donor continued to donate while we were testing, and continued to donate negative, serology negative and PCR negative units over time.

They entered the clinical study, and they were anti-core positive. This sample here, which we sent out, was one of the ones in the category negative for anti-HBs, negative for anti-core. We also sent these two units and

this unit over to our research laboratory in Germany. We did this in a pool system, so one of the questions is, well, maybe because you used the pool system, that is why you got a negative and you lost the signal. We tested these units straight, no dilution. They got the identical results that we got in the pool system. The positives were still positive and the negative unit was negative. Next slide, please.

So as far as our conclusion, we find that the PCR testing for hepatitis B increases our safety margin by removing units that we would not normally remove before they go into production. We find that the signal, the PCR signal, is earlier than the serology signal. We are able to identify units that contain virus that are not otherwise going to be identified. And we also found that the positive signal seems to disappear and is not consistent.

So, as far as the bottom line goes, as far as we are concerned, we believe that NAT testing is a benefit to both our donors and the recipients of our product, and it does increase our safety margin. And I thank the committee for letting us present this data.

DR. HOLLINGER: Any comments to Dr. Watson?

[No response.]

DR. HOLLINGER: Okay.. The next presenter is Larry Mimms from Gen-Probe. Larry?

DR. MIMMS: I know it is getting late. In the interest of time, I will try to move through this relatively quickly. I am Larry Mimms from Gen-Probe. We have been in business for about 17 years, dedicated to Nucleic Acid Testing. We have been developing an HIV-1/HCV assay for donor screening. I think most of you are aware of that. About 70 percent of the U.S. blood supply is being tested today using that test. We have also been working on a high throughput TMA assay for HBV DNA detection. Next slide.

Let me go right away to the data. The technology and the methodology is similar to that currently--that test that is being used under IND. That is the HIV-1/HCV assay.

Two ways we look at sensitivity for the HBV transcription mediated amplification assay. We look at sensitivity panels. We also look at seroconversion panels. And let me show you the sensitivity panel data first.

We use the Euro Hep panel to quantify our panel. This is obtained from the Euro Hep agency. I think there is also being developed a World Health Organization standard. So like all of the Nucleic Acid Testing, we really need to develop standardization so that we can compare sensitivity across assays.

A recent publication showed that one Euro Hep unit is equivalent to three copies per mL, so you can see that our positivity rate--we run a large number of replicates,

that is what the N represents at each of these levels of panel--you can see that at 18 6 Euro Hep or about 18 copies per mL, we have a 44 percent hit rate or positivity rate. At 75 copies or at 25 Euro Hep units per mL, we are about 92 percent hit rate. Next slide.

That is the Ay panel. We also had similar results from the Ad W panel. Specificity is obviously critically important. We have run 1,034 samples. These were surface antigen negative fresh frozen plasma from Gary Tegmeier's lab at Kansas City. We had an initial reactive rate of 4.8 percent and a repeat reactive rate of zero percent. Next slide.

We have run a large number of--these are 18 commercially available seroconversion panels that Mike Busch referred to earlier. Some of these are from Bioclinical Partners; others are from BBI. And this is a comparison on the Y axis, the number of days earlier that we can detect HBV by the TMA assay compared to the monoclonal Auszyme dynamic assay from Abbott, and anywhere from 4 to 27 days earlier for most of those bleeds.

There was one interesting sample, and I will show you further data on that later, 93 days earlier detection. So if you exclude the 93 days, on average we can detect HBV DNA 16 days earlier than the current licensed monoclonal Auszyme test. Next slide.

We believe the most sensitive surface antigen test that is likely to be out there probably in the near future is the PRISM surface antigen assay, and in this case we detect HBV DNA earlier in all cases, anywhere from--or equivalent--from zero days to 27 days earlier, again with one interesting sample at 93 days. So on average 14.4 days earlier. Next slide.

Let me just show you, this particular donor we obtained, these are serial bleeds, a total of 26 over the period from December of '95 through April of '96. You can see that the surface antigenemia is detectable at bleed 20 with low level S/CO values by both Abbott PRISM and Abbott monoclonal Auszyme.

However, you will note we ran in replicates of two, and I am showing you the S/CO values for HBV TMA for those two replicates, at each of those bleed dates, and you can see that there is sporadic positivity, but it is positive even from the earliest bleed that was available from this donor. We don't know how much earlier, obviously, we would have been able to detect HBV DNA, but the difference in time from 12/17 to 3/20 is 93 days.

And, as you can see, low level S/COs with some, either two out of two or one out of two, reactivity rate. So we would judge that the concentration is less than 100 copies per mL in this early viremia period. And I think

Mike has reported earlier some interesting low level sporadic viremia in that so-called eclipse phase for HIV and HCV.

So, in conclusion, we believe that the seroconversion window can be substantially reduced using an HBV DNA test, by an average of 14 to 16 days compared to current surface antigen technology, and that that window period can be a very extensive length of time, even up to three months in this case. And then finally I would like to thank National Heart, Lung and Blood, who is partially funding this project, and also Wesley Stringfellow, whose group generated these data.

Thank you.

DR. HOLLINGER: Larry, you showed, on the last slide you showed two sample cutoffs again. I mean, what were the differences between those two?

DR. MIMMS: Those were just two replicates.

DR. HOLLINGER: So it--

DR. MIMMS: It is the same test, just two replicates.

DR. HOLLINGER: So one was very positive and--

DR. MIMMS: One can be negative.

DR. HOLLINGER: --like the second one down, one was very positive and one was negative.

DR. MIMMS: That is what we see in these kinds--

when you get down to these very low levels of viremia. We see an all-or-nothing type of reaction. It is kind of a quantum effect. The virus is there. We detect it with high S/CO. If it is not captured, if it is not amplified, then we get no signal. And this is typical of what we see in, whether it is a PCR assay or a TMA assay, you tend to see an all-or-nothing, especially in these qualitative assays. You know, in a quantitative assay you can modulate the signal, but we have chosen not to do that for the qualitative assays.

DR. HOLLINGER: But 25 sample to cutoff is pretty high. I mean, that is not a low cutoff.

DR. MIMMS: I should say that we get saturating signals in this assay at 25 S/CO, even at a 10 to 20 copy level.

DR. HOLLINGER: I hear you. Thank you.

Any other questions for Dr. Mimms?

[No response.]

DR. HOLLINGER: Okay. Thank you, Larry.

Several other people have asked to speak here on this issue. The first is Celso Bianco.

DR. BIANCO: We heard a substantial amount of very good information. However, I think that the concern that ABC members would like to express here is the need for many more studies that would define the benefits that the

hepatitis B testing, DNA recognition by NAT, would bring, before we place a tremendous amount of effort into a research study of that type. We are very happy with the ways HIV and HCV have developed, but we would like to continue placing our efforts in those where the benefits have been measurable and excellent before we jump into the next test. Thank you.

DR. HOLLINGER: Thank you. Dr. Katz? You had your name down to say something. Just give us your name and title, if you want, and you can sit down.

DR. KATZ: No, I have no prepared statement from AABB. As a blood center medical director, I think I have heard conflicting data here that I am having a difficult time reconciling. But the take-home point seems to be that the sensitivity is laying in single donor testing, and I don't believe that we are prepared to do that as an industry yet.

DR. HOLLINGER: Thanks, Louis.

Mike, do you have something?

DR. BUSCH: Just one comment. There is some disparity in what we have been looking at, but I think it may be explainable. The panels that we have classically studied for all these viruses have been classic seroconversion panels where the donors, these plasma donors have evolved to antibody for HIV or HCV or to full surface

antigen conversion, and those are the panels that a lot of the data we initially generate focus back on and try to understand the early dynamics.

And one of the other issues is, those historical panels, because the plasma industry didn't previously have a requirement that they save panels for months prior to release into pooling, they tended to date back only several weeks or so prior to antibody or antigen conversion. Now what we are seeing is a different kind of panel. As the industry has implemented antigen for HIV or now Nucleic Acid Testing, they are picking up donors who are no longer seroconverting, they are NAT converting. Many of them aren't even followed through seroconversion.

And now we have samples available for months prior to NAT conversion, and we are beginning to see some surprising findings of low level viremia that can extend back several months or weeks and be transient. So I think that, you know, I am not--I personally think that there is more to be learned as we move on, and we would hopefully understand that. On the other hand, most of what we are seeing in this early low level viremia for all three viruses, sort of unexpected, is very low titer and is not--for HBV--is not the kind of signal that we could pick up with minipool testing.

DR. HOLLINGER: Thank you.

There is a Mr. Nathan Kobrinski.

DR. KOBRINSKI: Mr. Chairman and committee members, I am Nathan Kobrinski. I am the hemophilia director for North Dakota, and I would like to thank Aventis for sponsoring my travel here.

The reason I wanted to come is, I want to go back to my experience in Canada, where I was the hemophilia director from 1980 to 1989, and I want to focus on the question of fail-safe, specifically on the question of a tragedy that happened in Canada in 1985. At that time in Canada, certainly in Manitoba, there was a general suspicion of concentrated blood products. We used cryoprecipitate primarily for hemophilia patients, and we had a very low level of seroconversions for HIV.

And as this problem became increasingly evident, we decided that we would tell our hemophilia patients they should only treat for life-threatening bleeds and absolutely necessary surgery. And that was the scene in 1985 when I faced the first heat-treated product. I treated two young children with heat-treated product. They were very--you know, the family was very excited about it because it was now finally safe. They both seroconverted, and they have since both died.

What relevance is that to today? Very simply put, all of the inactivation processes have the potential for

human error, just as my two patients lost their lives because of human error, or shall we say industrial error, or whatever. And so I make a plea to you, in thinking about the importance of the safety of the blood resource as it goes in to testing. Before it is disseminated to our patients, it must be pure. I don't want to see any more of those patients die in that way.

These methods are very exciting that we have heard this afternoon on PCR testing, and I am very reluctant to see these antigenemic phases that we are discovering, even in the absence of standard serologic safety measures, as being just dismissed. Please consider keeping them on, developing them and instituting them, for all of the patients' benefit.

DR. HOLLINGER: Thank you.

I have a Mr. Mark Ballow?

DR. BALLOW: Mr. Chairman, ladies and gentlemen of the advisory panel, my name is Mark Ballow. I am Chief of Allergy and Clinical Immunology at Children's Hospital in Buffalo, which is part of the SUNY-Buffalo system in New York. My travel was supported by Aventis Behring, as well.

I am here as a clinician who takes care of patients with primary immune deficiency diseases. These patients encompass children as well as adults, and I can tell you that the number one question is, "Can these plasma-

derived products give me an infection?" And you know what? I can't guarantee them. I can't say 100 percent that these plasma-derived products like IVIG cannot potentially transmit some infectious agent. And I think that was emphasized today in a number of presentations, both in early afternoon and what we have recently heard, that in medicine you can never say never.

Now, I do tell them there have been a tremendous number of advances over the past decade, particularly over the past five years, in plasma-derived products, in making them safe. This is a partnership between the FDA and many of the manufacturers. But I have to say that, you know, whatever more we can do to make these plasma-derived products safer, we owe it to the public. We owe it to the patients, we owe it to their families, and we owe it to the public to do whatever we can.

And here I am talking about back-up, redundancy, duplication, overlap, whatever you want to call it to try to minimize, by the technology that we have--if we have the technology, and that is obviously the critical question, and something that you all as experts have to address. If we have the technology, then we should use it to try to make the blood supply as safe as we can for the public sector.

Thank you for this opportunity to address you.

DR. HOLLINGER: Thank you, Dr. Ballow.

The next person is Edgar Gonzales. Mr. Gonzales?

[No response.]

DR. HOLLINGER: Okay. Tom Moran?

[No response.]

DR. HOLLINGER: Okay. And Jason Babcock?

VOICE: That is for tomorrow.

DR. HOLLINGER: Well, that is what I thought, too. I was thinking that this was for tomorrow, since we talked about it, but I am just reading what is on the sheet here. I can continue to go ahead just introducing everybody in the audience. Sorry about that.

Well, then, is there anyone else from the audience that wants to make a comment here?

[No response.]

DR. HOLLINGER: How about from the committee, anybody?

[No response.]

DR. HOLLINGER: One think I just want to mention--excuse me, Toby--is I think we have to remember with hepatitis B, as distinct with some of the others, that because somebody receives a unit of blood that may be infectious, that doesn't--and I have said this before--it doesn't necessarily mean that something bad is going to happen to that person. Now, we know that only about four-tenths percent might develop fulminant hepatitis, and these

are people who are hospitalized.

So, if you look at these numbers and you say that perhaps 200 would be infected each year, and we have learned some data today that might suggest that with the newer HBs antigen tests, that perhaps you could pick up three-fourths of those, you will end up with about 50 per year. Four-tenths of those would be about two-tenths of a person, or about 1 out of 20 million recipients might die of fulminant hepatitis B by virtue of getting a positive unit of blood.

And then there are other scenarios. Half of the people are probably going to be dead within, will expire within three to five years, and we know that from many other studies, anywhere from 50 to 70 percent. Only about 1 to 5 percent of people who are actually infected will become chronically infected, and only about 20 percent of those will develop cirrhosis over 20 to 30 years.

So all of these things, I think, have to be taken into account, and sometimes we lose sight of the fact of thinking that just because a person gets an infected unit of blood, that that person is going to die, because a vast majority will probably not die. And it is really a relatively small number in many cases, particularly with B. That is what I am really talking about here, is hepatitis B. So we should never lose sight of that, that without downplaying that there are still risks here, but we ought to

be realistic about what these risks really are at this stage of the game.

Dr. Simon?

DR. SIMON: Well, this is only the follow-up to the question I asked before. It wasn't completely clear what the FDA was hoping to get out of this discussion, but I think it has been useful in terms of sensitizing us to the issues.

It would appear to me that the plasma industry is moving ahead, and I would assume that they are doing this under IND and, you know, with the approval and input of the agency. And from what we have heard, the blood centers wish not to move ahead, at least at this time, and I think could use the time to observe or learn from the experience in the plasma industry. And I guess I would think the status quo, if you will, is acceptable from that point of view, because progress is being made, and as we learn from it, then the blood centers can decide at what point they want to re-look at this issue.

DR. HOLLINGER: Dr. Boyle?

DR. BOYLE: I am going to prove that I didn't understand what I was listening to for the last three hours by asking two questions I would like to take away from this. Was I seeing that in the tests of the plasma using NAT, we were picking up cases that would not have been picked up

using standard non-NAT testing for each--for hepatitis B? That is question one.

Question two is, are we seeing the differences between the two sets of presentations because one is dealing with plasma and one is dealing with whole blood, or are we seeing it because we are comparing different tests? So those are the two questions I would like answers--

DR. HOLLINGER: Or different populations, plasma population, volunteer, versus whole blood population.

Somebody like to respond to that, the question first of all about the HBV DNA? You asked the question basically as where there is window period blood being picked up. Is that what you are asking? Ed? Dr. Tabor?

DR. TABOR: Well, let me try to answer that, but I am speaking for other people who gave presentations. The answer is yes, the HBV NAT is picking up some cases that are among donors that would not otherwise be detected. That is really the reason this is on the agenda, because we were surprised by the number that we were hearing about through the grapevine and through the INDs.

And in answer to your--but before I answer your second question, I want to point out, partly to balance what was said by one of the members of the public, that the inactivation and removal processes for plasma derivatives now are safe, obviously, when they are done correctly. But

there has been no transmission of hepatitis B virus by any plasma derivative for quite a number of years in the United States. Because even though some of the inactivation procedures that were put in place in the mid-'80s turned out, not due to human error but due to misjudgment of the efficacy of the processes.

In contrast to those, the processes that are in place now have been shown to be effective in inactivating and removing hepatitis B virus titers far greater than the amount that is present in any of the plasma, that could be present in any of the plasma going in. In fact, most of the products are made by processes that include at least two processes for removing and inactivating these viruses.

And in answer to your second question, I think I have to say we don't know. It is certainly a fascinating difference. These are fascinating differences that we have heard between the two groups of data, and I think we need more study, and studies are being done, as you have heard.

DR. BOYLE: Just the one question or one response is, although I am reassured about the no transmission, each of these meetings we hear about the problems of the GMPs, and all of it assumes GMPs are working well and so on, so--

DR. TABOR: Well, you are absolutely right. It does--I just thought that, to put it in perspective, it is important to say that we have not seen transmission; that in

addition to the test methods, we have the inactivation and removal. Obviously, everything depends on the GMPs being done correctly, and that is an area that the FDA is of course working on.

Dr. Koerper?

DR. KOERPER: I am not sure of the question that we are being asked. I wonder if--

DR. HOLLINGER: There is no question.

DR. KOERPER: Because I haven't seen a specific question.

DR. HOLLINGER: There is no question. There is no questions here. This is just information.

DR. KOERPER: Okay. Thank you.

DR. HOLLINGER: Thank you.

Dr. Macik?

DR. MACIK: With hepatitis B there is also another major difference between this and hepatitis C and HIV, and that is the vaccination program. And, as I understand it now, all children are vaccinated against hepatitis B, and unless somebody came back and gave me numbers of what the failure rate was of the vaccination program, we are also dealing with a process here that has a second fail-safe measure, particularly in the generations coming up, that doesn't presently exist with the other two products.

And I am not against, you know, screening and

trying to find and prevent blood from going through, but I think if the effort was put into a more massive vaccination process, that we wouldn't have hepatitis B or we should have very low levels of hepatitis B infection in the blood to begin with.

DR. HOLLINGER: I think the number is around 60 or 70 percent are being vaccinated. It is supposed to be universal, but I think those numbers are around 70 percent right now. But it is going up; they are moving up very rapidly.

Dr. Stroncek?

DR. STRONCEK: You know, my understanding is the tests done by the plasma groups were pooled HBV NAT assays, and we have heard other people say, well, it won't do any good to do pooled NAT HBV assays because we won't find anything, yet here we see a lot of data suggesting we will. My memory, it could be wrong, but as we went into NAT for HIV and HCV, we didn't have a lot of data. We didn't have studies saying it was effective. I think if we would have had this data now, we would have said, "Why not do HBV, too?" So maybe we need to say that we should quickly move into HBV testing. You know, it doesn't seem consistent to say, "No, we need to do more studies now."

DR. HOLLINGER: I think the issue, it seems like to me, is not so much whether they can do it or not. The

difference is whether they would have to do single donor testing versus pool testing. I think that seems to be one of the major issues.

Yes, Marion?

DR. KOERPER: My recollection from that earlier discussion was that the reason they weren't proposing NAT testing for HBV was that the level of viremia was lower in most individuals who were seroconverting, and therefore they would have to do single donor testing. So unless that has changed, I mean, it seems like from what I have heard, it seems like there is a few individuals who may have a high viremic load, but my understanding is that most individuals are fairly low and that is why the pooled testing is not as cost-effective.

DR. HOLLINGER: Yes, David?

DR. SCHMIDT: Well, I mean, from what I can tell, a lot of this data--you know, it is the same thing you did. They didn't want to do NAT testing on HBV because they didn't think we would shorted the window. Most of what I have seen from the REDS and other studies is extrapolation of data, which is the best you can do.

But now that the plasma groups got real data, it suggests that those extrapolations were wrong for whatever reason. So I think if you look at the hardest data, it is not good data, but the best real data we have, it suggests

that these assumptions that were made earlier about HBV or hepatitis B virus were wrong.

Dr. Nishioka?

DR. NISHIOKA: Lower antigen test, and by improving the testing reading, it double day by day, but in this NAT screen, right, using the test in smaller pool system at this point is critically important. That I wanted to say. And the system how to supply the blood after NAT testing is entered the system to be picked up.

DR. HOLLINGER: I want to call the committee's attention also to what I think is a very good summary, if you haven't already, many of probably already have. In Transfusion, I think it is March issue 2000. It could be--am I correct, it is March? February issue 2000. I think it is a real good review on NAT testing, looking at all the issues that are out there, talking about many of the assays. So if you haven't read it, I would recommend everyone looking at it, at least on the committee here.

I appreciate the committee's indulgence in going over. We are about 20, 25 minutes over what we said we would be, and I apologize for that. Tomorrow we are going to take up, again, committee updates. There is a session on a blood action plan, and then we have a session in the afternoon on a report of the intramural site--oh, I am sorry--donor deferral issues, which we have a question on,

and then there will be a report on the intramural site visit. We will start at 8:00 o'clock in the morning. Thank you all.

[Whereupon, at 6:25 p.m., the committee adjourned, to reconvene at 8:00 a.m. on Friday, March 17, 2000.]

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CERTIFICATE

I, **ELIZABETH L. WASSERMAN,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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