



U.S. Food and Drug Administration

Notice: Archived Document

The content in this document is provided on the FDA's website for reference purposes only. It was current when produced, but is no longer maintained and may be outdated.

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES

+ + + + +

FOOD AND DRUG ADMINISTRATION

+ + + + +

HEMOGLOBIN STANDARDS AND MAINTAINING
ADEQUATE IRON STORES IN BLOOD DONORS

+ + + + +

PUBLIC WORKSHOP

+ + + + +

WEDNESDAY
NOVEMBER 9, 2011

The Public Workshop convened in the Natcher Auditorium at the National Institutes of Health, 8800 Rockville Pike in Bethesda, Maryland at 8:30 a.m., Jay Epstein, Director, presiding.

PRESENT:

SESSION 1:

SIMONE GLYNN, MD, MPH, NHLBI, NIH

ORIEJI ILLOH, MD, DBA, OBRR, FDA

MOHANDAS NARLA, Dsc, PhD, New York Blood
Center

JOE KISS, MD, The Institute for Transfusion
Medicine

ALAN MAST, MD, PhD, Blood Center of
Wisconsin

BARBARA BRYANT, MD, University of Texas
Medical Branch

ANTHONY KELLER, MD, Australian Red Cross Blood
Service

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

MICHAEL P. BUSCH, MD, PhD, Blood Systems
Research Institute
BRIAN CUSTER, PhD, MPH, Blood Systems Research
Institute
HANY KAMEL, MD, Blood Systems Research
Institute
RICHARD FORSHEE, PhD, OBE, CBER, FDA
MERLYN H. SAYERS, MB, Bch, PhD, Carter
BloodCare
JED GORLIN, MD, MBA, Memorial Blood Center
MOHANDAS NARLA, DSc, New York Blood Center
RICHARD BENJAMIN, MD, PhD, FRCPATH, American
Red Cross
BARBARA ALVING, MD, USUHS, Moderator
RICHARD DAVEY, MD, FDA
HARVEY KLEIN, MD, NIH
JAY EPSTEIN, MD, OBRR, FDA

ALSO PRESENT:

RITCHARD CABLE, MD, American Red Cross
STEVE KLEINMAN, AABB
ANNE EDER, American Red Cross
KATHLEEN BAGSHAW, Children's National Medical
Center

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

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

Page

Session 1: Iron stores and Iron Deficiency in Blood Donors Moderator: Orieji Illoh, M.D.	
Introduction: Current practice and donor safety/blood supply issues Orieji Illoh, M.D., DBA/OBRR/FDA	7
New Insights into Iron Homeostasis Mohandas Narla, D.Sc., Ph.D., New York Blood Center	21
Measurement of iron stores in blood donors - methods available Joe Kiss, M.D., The Institute for Transfusion Medicine	48
Iron stores and iron deficiency in blood donors- REDS II Donor iron study Alan Mast, M.D., Ph.D., Blood Center of Wisconsin	89
Iron stores and iron replacement in blood donors Barbara Bryant, M.D., University of Texas Medical Branch	125
Effectiveness of post donation short term iron replacement in female whole blood donors Anthony Keller, M.D., Australian Red Cross Blood Service	162
Donor hemoglobin/ Iron status: BSRI data Michael P. Busch, M.D., Ph.D., Brian Custer, Ph.D., MPH, Hany Kamel, M.D., Blood Systems Research Institute	216
Impact of any changes in interdonation interval on blood availability Richard Forshee, Ph.D., OBE/CBER/FDA	227

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Predicting the effect that lengthening the red blood cell interdonation interval would have on community blood center inventory management	
Merlyn H Sayers, MB, B.Ch., Ph.D., Carter Blood Care	245
AABB Inter-organizational Task Force on Donor Hemoglobin: Update	
Jed Gorlin, M.D., Memorial Blood Center .	260
Panel discussion: Opportunities and barriers to maintaining adequate iron stores in blood donors- Interdonation interval, iron measurement, and iron replacement.	
Discussants: Mohandas Narla, D.Sc., Ph.D., Alan Mast, M.D, Joe Kiss, M.D., Richard Forshee, Ph.D., Jed Gorlin, M.D., Anthony Keller, M.D., Barbara Bryant, M.D. Michael P. Busch, M.D., Ph.D., Merlyn H Sayers, MB, B.Ch., Ph.D.	
Moderator: Barbara Alving, M.D.	272
Workshop summary	
Moderator: Harvey Klein. M.D.	334
Hemoglobin standards for blood donors in the US - Jed Gorlin, M.D.	335
Hemoglobin and iron measurement in blood donors- Harvey Klein, M.D.	342
Iron stores and iron deficiency in blood donors - Barbara Alving, M.D.	351
Conclusion and Adjournment	355

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

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

8:28 a.m.

DR. GLYNN: Well, I guess that's my signal this morning. So welcome, and good morning. I think we're going to have a great day today. We're going to start by reviewing iron homeostasis and methods available to us to measure iron stores in blood donors.

We will then review the magnitude of the problem, meaning the proportion of donors found to be iron deficient or depleted, whichever way you want to call this, and what effects that level of iron deficiency or depletion. So factors such as donation intensity, gender, age, et cetera.

We're then going to discuss potential mitigation measures, including the use of iron replacements or changes in the interdonation interval frequencies, and then we will also evaluate how maybe potential pilot studies or research could be conducted to evaluate these potential strategies that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

we'll be discussing, in terms of their impact not only on iron status but also on donation availability.

Then we will have a panel discussion led by Dr. Alving, to discuss physicians in greater depth, and answer questions. Of course, we will take also questions after each speaker if we do have the time.

Finally, at the end of the day, we'll have a workshop summary from each of the workshop panel moderators. So that's kind of the plan for the day. I was asked also to remind you to please complete your evaluation forms at the end of the day. This is something that's very important for I guess the FDA to look at.

Okay. Our first speaker is Dr. Illoh. Dr. Illoh joined the FDA in 2009 as a medical officer in the Division of Blood Applications. Prior to joining the FDA, Dr. Illoh practiced Clinical Pathology and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Transfusion Medicine at the University of Texas Medical School-Houston.

Dr. Illoh is going to provide an introduction to this morning's session, and talk to us about current practice and donor safety blood supply issues.

DR. ILLOH: Okay, good morning, and we're going to talk today about hemoglobin's big brother, iron, you know. He kept on coming into the way yesterday, so today is his day.

So I'm just going to give a brief introduction into today's discussion, and my outline includes an introduction. I'll talk a little bit about iron stores and blood donors, issues about iron depletion and deficiency, the interdonation interval, which is what we have right now, and then just a little bit on the previous public discussions discussing iron deficiency and blood donors. Then lastly, I'll go over the workshop objectives.

So today's part of the workshop, we

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

will be looking at the consideration between, the balance between donor safety again, and the blood supply. The donor safety issue that we want to address today is iron loss following frequent blood donation, something we all know about, and considering the fact that there are different mitigation measures for iron deficiency in blood donors, one of them is possibly addressing the interdonation interval. So if you still do that, it might impact the blood supply. Those are issues we'll be looking at.

So why are we looking at this issue? I think we all agree that addressing this issue might improve donor safety, either by allowing adequate time for iron recovery or instituting different measures that could mitigate iron deficiency in blood donors. So this is a little summary about iron depletion.

I think we all know this. Iron loss, of course, following blood donation. Frequent donations can lead to iron deficiency and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

possible subsequent anemia.

I think we've all agreed, after yesterday's discussion and previous discussions that hemoglobin testing is not an accurate measure of iron stores, and that possibly we need to consider strategies to mitigate iron deficiency in blood donors.

So there's the so what question again, you know, so what that people are iron deficient. You know, what's the evidence of any harm to the donors.

Well, it's known in the literature that iron deficiency in general causes adverse effects, and these could include anemia, fatigue, restless leg syndrome, possible cognitive impairment, depression and anxiety, and many more adverse effects that I have not mentioned here.

Now in blood donors, I think we all would argue or agree that there's limited information on the effect of iron deficiency in our blood donors. It's well known what

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

iron deficiency does in other groups of individuals or patients. There's also evidence that replacing iron in some of those people that have those symptoms does reverse the effects.

For example, some of you might be aware of a paper in Blood, where the authors administered IV iron to a woman who presented with fatigue, I think, and there was an improvement in symptoms of fatigue in the group that got IV iron, compared to those who didn't.

So you can look at all this information and make your own conclusions, but it does seem like iron deficiency does cause some clinical effects on individuals who have it.

However, there are reports in the literature suggesting a beneficial effect of low iron stores in males undergoing repeated phlebotomies, and I have some of the references down here. There have been reports

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

of a favorable lipoprotein profile, compared to non-blood donors, a lower risk of cardiovascular disease, and a possible reduction of iron-induced oxidative stress. So you can look at the literature and make your own judgment on that.

So if you feel that iron loss in blood donors is a problem, how can that be fixed? I have three bullet points here. You might have other ideas. One way could be to allow for adequate time for iron recovery. So that's looking at the interdonation interval.

Or you could test the donors for iron stores and check for those who are iron deficient and then deal with that. Now dealing with a low ferritin level could take another day of discussion, you know, who should you test, how you should handle it, how often should you do the testing, and I think we'll discuss some of that today. Or you could consider iron replacement following blood donations, and that again is another

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

discussion. Who should get iron replacement, how often, who should administer it and things like that.

So I'll talk a little bit more about the interdonation interval, because that's what we have right now. Just a reminder, that the interdonation interval is in place to ensure donor safety, by allowing adequate time for red cell recovery, not iron recovery per se. Iron does recover to some extent, but really within eight weeks, you have some degree of, a significant degree of red cell recovery.

So currently in the regulations, we have a requirement that a person may not serve as a source of whole blood more than once every eight weeks, and we do know also that we have guidance documents that address double red cell donations, for example, where we give a 16 week period for recovery.

So if you increase the interdonation interval, it might decrease the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

risk of iron deficiency, basically by allowing more time for iron recovery. We've, I think Brian shared some data that might give us an idea of, you know, how long we should wait and whether that's acceptable or not. That's another discussion.

So by so allowing our donors to recover their iron, it may decrease future donor deferral for low hemoglobin, because they're allowing them to recover their iron and therefore recover their hemoglobin levels adequately. But we do know that adjusting the intervals will adversely affect the blood supply.

So how will this affect the blood supply? It kind of goes with what I said yesterday. It can negatively affect the supply of the following red blood cells, especially your O negatives. So they're very essential, and other rare phenotypes.

It can also affect your collections that you obtain by apheresis, including double

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

red cells, and it may also affect the availability of donors for reagent manufacturers, and there are many more that we will hear later on today.

Now once again, I'm going to go over the international standards, and like I mentioned yesterday, when you look at these standards in different countries, you have to take into account that they all have maybe different methods by which they -- their collection volumes, for example, how they address iron deficiency in their blood donors. So these all vary.

But in those countries that have single hemoglobin standards, including the U.S., you can see that the interdonation interval varies. We have 56 days both in the U.S. and Canada. However, Switzerland limits donations to three times a year for women and four times a year for men.

Those that have gender-specific standards, for example, a hemoglobin of 13 for

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

males and 12 for females, you can see it varies also. 56 days, but a limitation of four times a year for women and six times a year for men in France. 84 days for all in Australia, and 90 days in Israel.

In those countries that have a standard of 13.5 grams per males and 12.5 for females, once you can see their interdonation interval varies, and you know, once you have to ask what is their intention?

Are they putting this in place to allow for red cell recovery, or for recovery of iron stores. You can see it varies. Note the UK. 84 days is acceptable, but they recommend 112 days.

Lastly, Brazil and Hong Kong, showed this data yesterday, and this is their interdonation interval, limiting donations to three times a year for women, four for men in Hong Kong, and the same thing in Brazil.

So lastly I'll go over previous public discussions concerning this issue.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Like I mentioned yesterday, this has been a long-standing discussion. This is not new. In 2001, there was a workshop that discussed maintaining iron balance in women blood donors of child-bearing age.

In this workshop, they discussed iron deficiency in female pre-menopausal blood donors in particular. They discussed the medical issues leading to iron replacement, and iron replacement and possible protocols. So at the end of this workshop, the conclusion was that there should be a research program on iron replacement.

I'm not sure how far that went, but I'm not aware of anything that came out of that workshop concerning the research program, but maybe somebody else can correct me if there's something else that was done.

Then I talked about the proposed rule yesterday, where we asked for several comments, and I'm not going to go over everything. But I'll just mention the first

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

bullet which is relevant to our discussion today. We did ask on comments for data on increasing the interdonation interval, and I also showed this slide yesterday.

But what I want to outline here is that concerning the interdonation interval, the comments included a request to wait for the results of the REDS II study on iron status in blood donors, and that will be discussed today.

I talked about the other bullet points yesterday, recommending dropping the hemoglobin requirement for females to 12, or disagreement about that requirement of dropping the hemoglobin to 12.

Then there was a Blood Products Advisory Committee meeting in September 2008 that discussed iron status in blood donors. Basically, the same issues, same consideration of the different mitigation strategies. The committee members did agree that iron depletion in blood donors was a concern or is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

a concern. They did discuss testing for iron status in a donor study, including things like ferritin.

They discussed alternative strategies to mitigate iron depletion, including iron supplementation, dietary recommendations, changing the hemoglobin/hematocrit acceptance standards, which we discussed yesterday, and possibly modifying the interdonation interval.

Then I just want to include this also. At the Advisory Committee for Blood Safety and Availability in December 2008, there was a discussion about informed consent for blood donors. One of the recommendations that came out of that meeting was that blood establishments should include, or consider including in their consent forms the effects of repeat donation on the donor population, the gender-specific effects of iron deficiency on the donors, and the effects of collecting blood from anemic men using the current

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

donation thresholds, some of which we discussed yesterday.

Then finally at the BPAC meeting last year, concerning the interdonation interval, the committee recommended that we await the final results of the study on blood donors, which is the REDS II-RISE study, before considering any changes to the interdonation interval. I mentioned yesterday the votes concerning the hemoglobin requirements for male donors and female donors.

So the key things we'll be looking at today, just a summary, are basically donor safety issues and here today we'll be talking about iron deficiency due to frequent donations, and how to mitigate that, and then also considering the fact of interdonation interval adjustment could be one of those measures, the blood availability issues related to that.

So our objectives today are to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

discuss recent studies on iron status of blood donors, kind of also to get an overview about iron hemostasis, and then discuss strategies to maintain iron balance in blood donors.

So we will be reviewing testing methods available for iron stores, and review recent studies on iron supplementation in blood donors. We have the opportunity to have people from other countries also to share with us their experience. Then also discuss how changing the interdonation interval could affect blood availability.

So I think that's my last slide, and I can take any questions if there are any.

(No response.)

(Applause.)

DR. GLYNN: And so our next speaker is Dr. Narla. Dr. Narla received his doctorate degree from Washington University in St. Louis. He's currently Vice President for Research at the New York Blood Center. His research interests, I think you probably all

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

know that, during the last 35 years, have concentrated on developing detailed mechanistic insights into red cell function in health and disease.

So it's really a pleasure to have you, Dr. Narla, and you're going to be discussing new insights into iron homeostasis.

DR. NARLA: Thank you very much. First of all, I'd like to thank Dr. Rick Davey and the Planning Committee for asking me to participate in this meeting. When Rick asked me, I was really surprised, why am I being invited to this meeting, and I really don't know very much about it.

Although I worked in New York Blood Center for the last ten years, I've been only working on red cells and red cell disease. I have very little to do with blood donation. So I apologize to people that none of the data I present have anything to do with the blood donors.

But I was kind of excited to give

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

this talk, because I think over the last ten years, there's been explosive growth in our understanding of how iron is handled, and I thought I would review for you some of these new finding on iron homeostasis.

Just like when erythropoietin was discovered by Dr. Gene Goldwasser many years ago, how the evolution of our understanding of erythropoiesis, the recent discovery of this hormone hepcidin is really making huge impacts on our understanding of how we handle iron and iron homeostasis. So what I'm going to do is to review for you some recent data on hepcidin.

Before I do that, I really would like to thank my very good friend and colleague, Dr. Ella Nemeth from UCLA, and she and Tom Gantz, along with many, many other investigator who have really made major contributions to this area of research. She helped me a great deal in preparing this presentation.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So in erythropoiesis and iron, I guess we've been talking about iron and hemoglobin and red cells for the last day. Really interesting stuff, but basically each hemoglobin molecule has four iron atoms, and each mL of packed cells has about a milligram of iron.

So in five liters of blood, we are talking about about 2.4 grams of iron and circulating red cells in all of us. Since the red cells on average live for 120 days, and we need to make about -- we need about 2,400 milligrams in 120 days to replace, so we're talking about 20 milligrams for a day that we need, for maintaining baseline red cell production to replace the one percent that's being destroyed in the circulation.

As I said, erythropoietin, when it was discovered, really showed how erythropoietin-dependent, erythropoiesis happens in the bone marrow. But in the terminal erythroid differentiation where you

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

differentiate based on science of red cells, is strictly dependent on iron, because you're making a lot of hemoglobin and without iron, there's no hemoglobin.

So when you start talking about a global economy, we'll talk about iron economy this morning, and basically we have about 2.4 grams of hemoglobin in circulating red cells, and about a gram of hemoglobin in the liver in the stored, and about 3 to 4 milligrams is in the plasma iron pool that is in the circulating plasma pool.

So everyday, we are destroying about one percent of the cells. So we're getting about 20 milligrams of iron, that is from the microphages that are being, eating up iron in red cells, and is being released and will be able to reutilize that. This 20 milligrams then is used to make fresh red cells.

So we lose about 1 to 2 milligrams a day of iron due to various reasons,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

including sloughing off of cells, arterial cells and other cells. So we need on baseline and steady state, to make a normal amount of red cells, about one to two milligrams of iron has to be taken in.

So the problem is if you have too much iron, we get tissue and organ damage, and too little iron, we get cellular dysfunction, and as we have been talking about iron deficient anemia as well. In the plasma iron concentrations, this is the range for men and women, and you can see it's about, on the average, about 20 to 25 micromolar.

So as I said earlier, the big change has come, it's exactly about ten years ago that this hepcidin was first described. It's a iron regulatory-type hormone, and it is made in the liver, where it is made as 84 amino acid hepcidin, and then it's cleaved into 25 interacid bioactive hepcidin by furin.

When this was discovered, it was actually discovered as an antimicrobial

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

peptide, but very soon it became that it was very important for iron homeostasis.

What does hepcidin do? This is kind of information about when you inject hepcidin, for example, into mice, for 50 micrograms IP, then within an hour you can see the serum iron dramatically decreases.

Then over the next 6 to 24 hours, the serum iron comes back and the hepcidin is cleared from circulation. The other important thing was the first thing that came about about ten years ago, was when they made transgenic mice in France, with over expressing of hepcidin, you can see severe iron deficient anemia in these mice. So it was very clear that hepcidin is somehow playing a role in iron homeostasis.

Subsequently, what they discovered was ferroportin. Hepcidin was discovered first and then ferroportin, and what does ferroportin do? Ferroportin is a receptor that binds to hepcidin on cells that express,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

handle iron in our body.

So basically as I said earlier, we get about 0 to 5 milligrams of iron from the liver, and we absorb over 1 to 2 milligrams in the duodenum, and then 20 milligrams comes from the spleen and then 20 milligrams goes into the bone marrow to make red cells.

All the tissues that handle iron express ferroportin, and ferroportin is only cellular iron exporters in vertebrates. Peptide hormone is a ferroportin ligand. So hepcidin binds to ferroportin and is involved in the mechanism. I'll show you how.

So ferroportin is, as I said, the only cellular iron export in vertebrates. It exports iron into plasma from the duodenum, hepatocytes, macrophages in the placenta, and the ferroportin is a hepcidin receptor.

So this is an elegant study from Ella Nemeth again, where they express ferroportin on cell lines, and then where you have hepcidin, hepcidin binds to ferroportin,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

is internalized and degraded. So this is a cycling of binding of the ligand to the receptor and endocytosis, and clearing up of the hepcidin from the circulation.

So normally when you have low hepcidin levels, we take iron and the hepcidin basically creates the -- there's no degradation of low hepcidin concentration. So ferroportin functions as an iron exporter, and we get iron intake.

But we're now high hepcidin. Then what happens is the fact that the hepcidin binds to ferroportin, is degraded, and there is no ferroportin on the surface of these cells. So you do not get export of iron and you get accumulation of ferritin in the cells itself.

So very basically, the ferroportin, by binding to -- hepcidin, by binding to ferroportin, is constantly sensing what the levels of iron we need to export from various tissues.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

How is hepcidin regulated then? It's really a quite interesting but quite complicated, and still is a very whirlwind story, because as I said, all this data has come out in the last four or five years. But what is very clear is that there are three different mechanisms of hepcidin regulation.

One obviously is the iron signal itself. Somehow, the body is sensing how much iron is in the circulation of the body, and then that itself regulates. Just like when we are becoming anemic, the kidney senses hypoxia, and we make more erythropoietin. Similarly, whether we have less iron or more iron is sensed, and that regulates how much hepcidin we need to make to regulate homeostasis.

The second thing is more interesting. More recent data suggests erythropoietin signal itself is important. So how much iron is needed in the bone marrow to make red cells itself can regulate, and I'll

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

show you some data about that as well.

Finally, more interestingly also is the fact inflammation itself can regulate hepcidin levels, and that has implications, as I'll show you, in terms of anemia of inflammation itself.

So first, I'll briefly describe hepcidin regulation by iron itself. So if you look at hepcidin in the healthy subjects with iron stores, you can see there's a very nice relationship between hepcidin levels and ferritin. So this is both in men and women. This is only data I have about normal subjects for interest for the transfusion field. But I think in the future, we'll get a lot more information like that.

The second thing is in iron deficiency, hepcidin levels are very low. That's because you don't want very low levels. You can absorb more iron and replace iron into the circulation. So it makes sense that you have very low levels of hepcidin in iron

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

deficiency anemia.

Now if you give hepcidin response to oral iron, this is a study published recently as well, if you can give iron and then follow what is happening to serum iron and hepcidin levels, you can see you give iron. The serum iron goes up dramatically, very rapidly.

But then if you look at serum hepcidin and urinary hepcidin, there's about a 12 hour delay after the serum iron goes up, and then the liver makes hepcidin, to down-regulate this serum iron. So it's a very dynamic process, just like you get erythropoietin response after bleeding. Hepcidin is responding as a result of changes in this iron status.

Again, direct evidence for this kind of role of iron, hepcidin iron deficiency is there are very rare children who have iron deficiency, despite adequate dietary iron content. It's only partially corrected by

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

supplemental iron, suggesting there is some problem in the response of this anemia.

Then about two-three years ago, a number of, two different groups have identified mutations in this membrane proteins called TMPRSS6, and in the presence of these mutations, these individuals have very high levels of hepcidin in the circulation, and now you know why they're iron deficient. There are high levels of hepcidin, so the ferroportin is being degraded. They're not able to absorb iron, and they become iron deficient.

You can see this in this data set, where you actually see these very high levels of serum hepcidin in these patients with iron refractory iron deficiency anemia.

So what we're talking about is first, iron deficiency. Now the other issue is iron overload, and as most of you know, hereditary hemochromatosis, we heard yesterday, at least a good blood donors for us

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

to use more blood. But unfortunately for them, it's a real significant problem, because they have excess iron absorption, and the deposition of iron in the liver, endocrine glands and heart, and it's really important to get rid of this iron, in terms of taking care of these patients.

What is again, what you'd expect from what I told you is in this case, you had to have -- the serum hepcidin levels should be very low, because that will account for increased absorption of iron. So in the case of hemochromatosis, you basically have very low levels of iron.

In fact, in spite of the fact there's high iron already in the circulation, high ferritins, but somehow there's a dysregulation of hepcidin, and they're not compensating. They're not making more hepcidin; they're actually making less hepcidin, resulting in more iron absorption, in spite of high tissue iron.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So a number of groups have been working on this, and a number of different mutations have been identified. The first one was HFE. Then there's transfer receptor two, another molecule called hemojuvelin, and these are all involved in the regulation of hepcidin production by the liver hepatocytes.

I didn't want to bother you with a lot about expression data from these things, but I can tell these three molecules are quite important in regulation of hepcidin by hepatocytes.

Of course, there are also rare mutations described in ferroportin itself, because you can see the ferroportin is mutated. It is not able to bind with hepcidin. You'd also have the same phenotype.

So either way, by either making mutations in hepcidin or, regulation of hepcidin production of the mutations that is simply solved, you can get the same phenotype, which is iron overload.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So now I'm going to briefly discuss with you how the second aspect of hepcidin regulation, which is erythropoiesis itself. So the iron loading anemias beta-thalassemia, congenital diserythropoietic anemia, some X-linked sideroblastic anemias are all situations where we get iron overloading, and it's mostly due to ineffective erythropoiesis.

That is, in the bone marrow, when we normally have conditions giving rise to 16 or 32 reticular sites, in these conditions you don't get complete maturation, and there's a lot of destruction and apoptosis of erythroid cells during terminal erythroid differentiation.

What is important to note in some of these beta-thalassemia intermediate patients, is they get iron overload even though they don't get any transfusions. So it's basically they're getting iron overload just in a natural way, as a part of the disease process, and this is a major cause of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

morbidity and mortality in these individuals.

So if you measure basically hepcidin levels in these thalassemia intermediate patients who are not getting any transfusion, you can see there's a significant reduction in hepcidin levels, and that's the reason they're absorbing more iron, in spite of the fact they're iron overloaded again.

If you now compare that with thalassemia measure, who are constantly being transfused because they are not making enough red cells, you can see the hepcidin levels are higher actually. The reason is we are suppressing erythropoiesis in these individuals, in contrast to the ineffective erythropoiesis.

So the idea is with all transfusions, there's a great need for erythropoiesis and that itself is subsiding, reducing the hepcidin levels, and you can have a normal amount incoming from the diet, so they're accumulating iron in the tissues.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Whereas in thalassemia measure, by transfusing the suppressing erythropoiesis, there's no erythropoietic signal on hepcidin, so in fact, and they're also iron overloaded.

So the hepcidin levels are higher, and so you're not absorbing more iron through the process.

Finally briefly, I'd like to talk about hepcidin in infection and inflammation, which is also a very interesting recent development, and here, these are a couple of papers published about our hepcidin. This work was done to really understand the regulation of hepcidin in the liver.

So what people did in humans is to really lower levels of LPS, and you can see within after three hours, you get a dramatic increase in hepcidin, urine hepcidin, and same thing is also true with the cytokine IL-6. You inject IL-6, and then again two hours post-infusion, you get a significant increase in hepcidin levels.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

There's a consequence. You see a decrease in serum iron in both cases. That is, these cytokines or inflammation is inducing tight regulation of hepcidin production.

And in fact, if you look at infection inflammation, you can see the hepcidin levels are about order of magnitude higher than control values, and this is also true in intensive care units, where you have high hepcidin levels.

In fact, some recent data suggests that elevated hepcidin is the cause of anemia of inflammation. Again, I want to be very clear. These are kind of new data, and we really have to do a lot more studies to validate all these things.

But I think there's overwhelming evidence that hepcidin regulation is playing a very important, it may not be the only regulator, but a very key regulator of iron homeostasis in a lot of different conditions.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So to kind of summarize, basically we have normal hepcidin levels of your normal homeostasis, and when the plasma iron levels go down, then we get iron deficiency anemia and anemia of inflammation with high hepcidin levels. Then we also get hereditary hemochromatosis and iron loading anemias in the other case.

So I think in the next few years, I think you're going to be hearing a lot of hepcidin and hepcidin regulation, and I think it makes a lot of sense, just like how erythropoietin has helped us to understand erythropoiesis. I think hepcidin is going to do a lot, in terms of our understanding, of how we handle iron in both normals as well as in inflammation and in various pathologies.

So to summarize then, hepcidin control system and iron homeostasis then is hemostatically regulated by iron, and hepcidin is decreasing iron deficiency and increasing iron excess, and there's a normal response.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

But this regulation of hepcidin causes common diseases. Hepcidin deficiency is responsible for hereditary hemochromatosis and iron overloading anemias, while hepcidin excess is anemia of inflammation and iron-refractory iron-deficiency anemia.

I just wanted to say, although all this great science has come through, we still really don't have a test that can be routinely used in a lot of research labs that are doing it, and some of the other people are developing.

I think that will be very important in the future for us, to really make this much more practical and really expand our understanding in a general sense. We need a really very good reliable test that is FDA-approved, so that we can trust that this can be used on a routine basis.

I think the second thing is there also is a lot of interest now in developing therapeutics based on this understanding as

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

well, hepcidin antagonists or hepcidin itself, in treating some of these low iron deficiencies and things.

So I think hopefully in the next five years, you'll hear a lot about that, and I'm hoping, after listening to all the wonderful talks about our problems with iron deficiency, with repeat donations and now hopefully at least hepcidin will help us a little bit, along with ferritin, in trying to sort out what is happening in these individuals and things. So thank you very much.

(Applause.)

DR. GLYNN: Mike.

DR. BUSCH: Hi Mohan. Thank you. That was really excellent, and two questions. One is the hemochromatosis polymorphisms or mutations, I wasn't clear on how those influenced hepcidin functionality. Is that understood?

DR. NARLA: Basically, a lot of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

mutations I talked about are expressed or are acting directly on hepcidin regulation, okay.

So you know, these molecules are very much in war in the production of hepcidin by the hepatocytes. It's very complex. I had a slide on it but I took it out.

But it's very well worked out how it's a BMP for pathway, bone morphogenic factor for pathway, and all these receptors, the Tmprss6 and transferrin receptors are all signaling to the hepatocyte to either make or not make hepcidin.

DR. BUSCH: Great, and then, you know, measuring hepcidin or ferritin levels, those are plasma parameters that you'd have to measure longitudinally, like in the context of a blood donation.

But I'm wondering to what extent would you predict that genetic polymorphisms that control iron or others, they might be able to either inform our understanding of the set point of hemoglobin in different racial

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

ethnic groups, or be useful in setting donor interval criteria.

DR. NARLA: As you know, that's a very active area of investigation, Mike. Actually, there's a couple of papers in the last year, year and a half, in *Nature Genetics* and others, where they have been doing this genome, GWAS studies, okay, on a large 20,000, 30,000 so-called normal individuals, and trying to relate at least snips in these genes.

Like there's very good evidence, the TMPRSS6, which is the one I talked about in iron deficiency refractive anemia, that have polymorphisms in that TMPRSS6, that correlates with MCV and MCH and things like that.

So I think it's very clear that you're right, that I think this whole pathway is going to make an effect on iron handling and MCV and MCH and red cell count and stuff like that. So the data is very preliminary,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

but it's very, you know, suggestive that there is genetic modulation of red cell parameters in normal individuals, yes.

DR. CABLE: Ritch Cable. I very much enjoyed your talk, and I couldn't help but notice that the slide where you showed oral iron resulted, was it four hours later, in a spike in hepcidin?

DR. NARLA: Right.

DR. CABLE: I'm wondering, that sounds to me like it might inhibit, you know, the absorption of that oral iron.

DR. NARLA: But first, you know, it goes in, but then it's a feedback loop. So the hepatocytes have to sense, to get the signal to make or not make hepcidin.

DR. CABLE: So I'm wondering if that response, and particularly a variability in that response in blood donors, may somehow impact the efficacy of iron supplementation?

DR. NARLA: Absolutely, absolutely.

DR. CABLE: In getting the iron to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

the body.

DR. NARLA: Sure.

DR. CABLE: And then speculating on, you know, getting around that with intravenous iron.

DR. NARLA: Yes. I think at the same time, I'll be very careful. Although there is some very plausible and very good evidence that hepcidin is very important for this regulation, the variations and dynamics of this, we really need to do a lot more studies.

One of the problems, as I mentioned, is the fact that we have very few labs, you know, that are doing hepcidin assays that we be comfortable with and confident about. I think once that is established, I think all the questions are very important and would be addressed in a fashion you'd be comfortable with.

DR. CABLE: I mean I think hematologists have known for some time it's

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

fairly difficult to treat iron deficiency anemia, and get iron in let's say the woman. We are about to embark on maybe trying iron supplementation in donors, and so the difficulties of getting iron through the GI tract into the body will be important.

DR. NARLA: Sure, sure.

DR. SAYERS: What is happening in those rare circumstances where there's dietary iron overload, like bond to this real hemosiderosis?

DR. NARLA: I don't know the answer for that, sir. Sorry.

DR. GLYNN: Actually, Alan was ignoring me, Dr. Mast. Would you be willing to mention a few things that you're doing with hepcidin in REDS?

(Off mic comment.)

DR. NARLA: We talked about, and he said he's going to talk about it.

DR. GLYNN: Perfect. Okay. Thank you. All right. So our next speaker is Dr.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

Kiss. Dr. Kiss is the Medical Director of Therapeutic Hemapheresis and Blood Services at the Institute for Transfusion Medicine in Pittsburgh.

He also carries an appointment as Associate Professor of Medicine in the Division of Hematology/Oncology at the University of Pittsburgh, where he practices and teaches consultative hematology. Because I'm the branch chief at NHLBI for Transfusion Medicine and Cellular Therapeutics, I will also mention that he's actively involved in several of our NHLBI-funded research programs.

In particular, the Transfusion Medicine and Hemostasis Clinical Trials Network, as well as the REDS II and the REDS III programs. So Joe will be reviewing the methods that are currently available to measure iron stores in blood donors.

DR. KISS: Thank you very much, Simone, and I also want to extend my gratitude to Dr. Davey for asking me to be here today.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

It's my pleasure to be here and talk to you about methodologies involved in measuring iron, and we use it in clinical circumstances and it can also be applied to donors, and the approach I'm going to take is to kind of summarize what's been done, and what hopefully will arrive at a destination that will tell us what maybe we should be doing.

So we'll start with an entire review of the field, and I'll just start off by saying that any time you see a list of entities on a slide, tests that could be done for iron deficiency means that there is no perfect test. All the testing that we do has certain side effects or certain cost-associated technical performance issues.

The first statement there, as we know, as we've heard repeatedly, that the pre-donation hemoglobin level is a late manifestation. So it's not necessarily -- it doesn't tell us anything; it just tells us too late, and we'd like to detect that before.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

There's a lot of work now being done with pre-anemia iron deficiency, that can lead to some of the side effects that we've been talking about, and that Dr. Illoh has mentioned earlier.

So the theme for this will be to kind of review these, describe the test, describe the methodologies involved. I'm going to have -- my slant will be towards the blood donor applications, and then I'll finish up with talking to you about what we decided to do in the RISE study, to look at methodologies, to look at iron status, and come up with some suggestions that are more prescriptive, rather than descriptive.

So I just want to start off by saying that as you heard, plasma -- there are a lot of proteins involved in our metabolism.

Transferrin was identified early as a transport protein. We can measure it and we've measured it for decades in the clinical hematology laboratory.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

What we know about it is that it saturates -- serum iron saturates the circulating iron transferrin. Normally, it's about 20 to 50 percent saturated. Levels below 20 percent or so tell us that the subject may be iron deficient.

However, this is also a relatively late development in the diagnosis of iron deficiency, and many blood donors would already have a low iron by the time they become deferrable or anemic.

So it's not all that helpful, although it has been used in clinical studies as a measure of iron deficient erythropoiesis.

What we do use, though, in conjunction with this in clinical hematology is ferritin. Ferritin is the iron storage vehicle in the body. It equilibrates with levels of iron in the bone marrow, and it can absorb, essentially hold very many molecules of iron.

One of the problems in clinical hematology, some of the factors that were

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

mentioned earlier -- IL-6 and things like that -- raise the levels of the protein, and we can measure this as a falsely elevated, even people with iron deficiency, because it's an acute phase response protein.

However, we're fortunate enough that we ask donors that they ask, they tell us that they feel well and healthy to donate. So the incidence of inflammatory diseases are relatively low in blood donors, and the relative incidence is low. So it certainly would be helpful from that end of it.

We don't have the complications of clinical medicine on top of normal donors, although we do accept donors, as we know, with arthritis and some other conditions. But it would tell us that that would not be a significant problem.

Now in using ferritin levels, we need to know what level marks or what level of deficiency we're interested in, and what is the level that we use to inform us about iron

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

deficiency. The classic cutoff of 12 micrograms per liter or nanogram per mL -- those are interchangeable units -- was based on early studies before ferritin levels were standardized.

These correlated with absent bone marrow iron stores, about 12 micrograms per liter. Subsequent analyses such as this one I'm giving you here have really targeted at slightly higher but in the same ballpark. I will show you normal levels in a minute. But basically about 15 gives us a pretty good classification of iron-replete and iron-deficient subjects, and that's also carried through on studies like this.

Dr. Cable showed you a ROC study yesterday. ROC studies are very useful pictorial depictions of sensitivity and specificity. The best tests are up here to the left. An area under the curve of one would be straight up. The right angle here would basically be a test that's 100 percent

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

sensitive and 100 percent specific.

So anything that's above this line is good, above a midline here, the imaginary midline that you see here. This is a study that was done that analyzed a number of studies.

It wasn't a meta-analysis, but it was a systematic review, high quality. They had selection criteria for high quality studies. Bone marrow iron, they also gave iron and saw a response. So they're really sure that the subjects were iron-deficient.

Ferritin values informed a lot of these, fewer values for some of the other analytes that were looked at here. The area under the curve for ferritin was the best of all these tests, and they looked at mean cell volume, transference saturation, RDW, and then protoporphyrin.

I'm going to mention protoporphyrin a little bit later. So you'll see protoporphyrin is this curve here, with

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

ferritin really outshone all these studies, in terms of sensitivity and specificity in a clinically defined group of patients with bone marrow, with iron deficiency. They too centered on about a 15 -- confirms the diagnosis of iron deficiency.

Now other studies that have been performed in the literature reflect that even higher levels of ferritin can tell us that the subject or the donor, perhaps, is iron deficient. This gets us to a different level.

Instead of just absent iron stores, it gets us to the level where the tissues are actually starved for iron. There is tissue iron deficiency.

What I want to just mention here is an aside, an editorial comment, is we know a lot or lot of this has been related to iron deficiency anemia, the hematologic consequences of iron deficiency. But there's much less known about these levels, in terms of the other potential health consequences of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

iron deficiency.

So we heard about fatigue. We heard about Pica. We heard about restless legs and we heard about cognitive issues, potentially in donors. These are non-hematologic manifestations mostly, if you will, CNS or neurologic manifestations.

We know a lot about erythropoiesis in iron, but the iron controls on the neurologic function are much less well-understood. So we need some help, perhaps, from neuroscience and neurobiology in answering those questions.

But levels of -- higher levels of ferritin can also reflect tissue iron deprivation, and the reason we know that is studies that have been done with the serum transferrin receptor. So serum transferrin receptors is another analyte that can be used in research studies.

These are showing early erythroid cells from normoblasts in the bone marrow.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Most of the transferrin receptors, the transferrin receptors are situated according to the need of tissues for iron.

They basically guide the entry of iron into the cell, and 80 to 90 percent of tissue transferrin receptors are in the erythroid series, but they're also in muscle, they're also in liver and they're also in brain.

When cells are -- either have high, when there's a lot of erythropoietic activity, there's more transferrin receptor available, and some of this is shed into the blood. So the baseline erythropoietic activity tells us something about these levels.

But in addition, if one becomes iron deficient or if an animal becomes iron deficient, these levels are shed into the blood and can be measured as a soluble transferrin receptor. So the soluble transferrin receptor is a truncated or shed form of the receptor, and if it's shed --

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

there's increased erythropoietic.

So some of these anemias that we deal with as hematologists will have high transferrin receptor levels. They don't really help us to diagnose iron deficiency. We don't expect that, because we screen blood donors, and -- but if they are, do become iron deficient, these receptors are up-regulated. They're shed into the blood, and they can inform us about tissue iron deficiency.

As you might expect, because of perhaps some underlying thalassemia, race raises these levels, and altitude. If you live at a higher altitude, more erythropoietic activity. So they really -- it's not necessarily a clinical test, but it's been useful in the laboratory.

The levels of these receptors or the measurement is not necessarily standardized. There's no international or uniform reference standards. So each lab or each manufacturer of a kit would have to do

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

the standardization, and you use their -- basically their reference range.

Then again, it's been used in research studies with ferritin, to define tissue iron deficiency. The seminal study on this was actually done by Barry Skikne and James Cook in Kansas a number of years ago, and I just want to talk you through this, because it teaches us a lot about how these receptors tell us about iron deficiency.

They bled -- much in the way of an accelerated blood donation program -- they bled subjects in the laboratory 250 mLs a week, until they became anemic. They actually dropped their hemoglobins by two grams and they stayed there -- took 17, you know, anywhere between 10 and 20 weeks to do this -- and they documented how much iron was lost, how much iron was potentially absorbed.

What you see here is on the Y axis here, is the ferritin levels and their subjects -- that is the ferritin, yes? -- the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

ferritin levels declining as the subject was bled. This was done every week, so if you think about this, it's basically a phlebotomy experience.

At this point here, which they basically said the subject was bled, there was no improvement in their hemoglobin. Their reticular sites count went to zero, they were iron deficient. They didn't do marrows, but they knew they were iron deficient by some other iron metabolism studies.

At this point, the ferritin comes down. It doesn't go down much further. This is basically a very low ferritin value in their subjects. The standard errors also come down. At the same time, transferrin starts to go up, probably as erythropoiesis starts to increase, as the retic count increases.

But it really -- it continues to go up after ferritin comes down here to zero. So basically, they were able to plot this as a log plot, and show a very nice linear function

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

between iron, between transfer receptor ferritin ratio -- which is what's being measured here -- and the iron status of the body.

It's hard to see this here, but the higher the ratio, the more negative the iron balance. So this is very useful, and we've actually applied this in blood donors as well, to tell us: well, how iron-deficient is someone? It's not just that they're iron deficient, but they're really iron deficient -- or a little bit iron deficient -- can be determined by this quantitative relationship.

Other studies have verified this, and I'm just going to show you two. This is one of Dr. Alan Mast's studies. It's a clinical study in anemic hospitalized patients, and this is basically correlating bone marrow iron with ferritin levels. The black dots here are the subjects with absent iron stores, and you'll note all of them had elevated serum transferrin receptor, and all

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

of them had ferritins. Basically, I drew the line down here to the X axis, down to about 30. So all of these subjects had ferritin values of 30 or less.

This is a study that's not done in hospitalized patients. This would be more akin to a bone marrow study. These were healthy non-anemic adults that were found to be iron deficient on the basis, not of their hemoglobin hematocrit, but on the basis of their serum transfer receptor levels.

They had two groups of subjects, those with high and those with normal levels, and the subjects with high levels here, indicating tissue iron restriction, all had ferritins less than 22. You'll notice in some of the subjects also with low ferritins did not have evidence of tissue iron deficiency, and so it's not a perfect test. But it certainly can tell us what level of ferritin is important in iron deficient subjects.

Now I've been asked specifically to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

talk a little bit about some other assays that are not in common use, but have been used in population studies of iron deficiency. One of them is zinc protoporphyrin or so-called free erythrocyte protoporphyrin.

I don't have a lot of experience with this test myself. Some of my colleagues in the REDS II program and RISE did have some experience with this. There is no real -- that I can find -- recent literature, but I'm going to tell you about the principle of the test and what we know about it in the iron deficiency blood donor setting.

So it's measured using a portable hematofluorometer, and the principle of the test is illustrated here. Porphyrin, the protoporphyrin going to is -- basically iron is added at the last step in the mitochondrion, to basically make HEM, the HEM molecule, which is then combined with globin to make hemoglobin.

Normally, we have iron available in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

this last step, and there's a ferric catalase enzyme that inserts the iron into the hemoglobin molecule -- those four atoms of iron inserted into every molecule that was shown to you earlier -- to make ferrous protoporphyrin combined with HEM and basically make hemoglobin.

If iron is deficient, zinc ions, as another divalent cation substitute, that changes the fluorescence of the molecule, and that could be measured as zinc protoporphyrin in a hematofluorometry system.

So this is not, I'm not meaning to say these are exclusively the manufacturers here, but these are two manufacturers that make this kind of equipment. Some of you may know it's been used in large population studies. It was originally thought it might be good test for early lead poisoning, because of changes in hemoglobin formation in lead toxicity.

But it's not really, I think, been

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

used extensively in that setting. Rather, lead levels are used these days. It has normal reference ranges, indeterminate and then high reference ranges. In a hospitalized patient, there are a lot of other things that can cause elevated zinc protoporphyrin levels, including increased erythropoietic activities such as with beta-thalassemia, lead poisoning, and even inflammatory disorders.

As I mentioned, there are limited studies on blood donors, and this was the best study I found. So I'm looking for promising studies here. There was a study that was reported, I believe, that might be a European study. Basically, they measured in 100 women blood donors to evaluate iron deficiency.

They found that the severely deficient, this classic definition of iron deficiency, had elevated ZPP values, and they scored, whether the ferritin or the ZPP value would predict deferral in a couple of donations. They found that the predictive

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

ability of the ZPP test was better than ferritin, 75 versus 26 percent in this group.

This is a relatively small study. I don't believe this has been confirmed, and then other studies give us data like this. This is a population study, looking screening for iron deficiency.

It's one of the NHANES studies that was done, and this is again a ROC curve, comparing hemoglobin to ZnPP, and they got this difference, that children with iron deficiency had abnormal ZnPP that were better than hemoglobin, but not in menstruating women.

So we have different data, some of which is conflicting, and relatively limited data on which to base recommendations for using this test. If you'll recall on the slide I showed you earlier, it was not better than ferritin in large scale studies of iron deficiency.

I want to turn my attention now to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

other measures, and these are measures we've adopted as part of the RISE study. Some of the newer technologies are -- were quite attractive to us, in terms of telling us, maybe giving us an early look at how donors become iron deficient.

We decided to look at a device. We actually employed the ADVIA 120 hematology analyzer, to look at sophisticated red blood cell indices, more sophisticated than just in MCV, but I'll show you that data as well. There are other technologies that can also look with a mature cell channel as well as a reticulocyte channel, to look at iron incorporation into both mature cells and reticulocytes.

So the principle of the test is that the mature cells, by analyzing various parameters of these cells -- and these are done with laser light -- one can look at early indications of decreased hemoglobinization of red blood cells.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So one analyte that I'm going to talk about the percent hypochromic mature cells, and this reflects iron incorporation during the three month life span of mature red cells. So if there's no iron when they're being made, this will be reflected as an increased percentage of hypochromic mature red blood cells.

Likewise, one can -- on a reticulocyte channel which was done with a different dye, one can look at incorporation of iron into reticulocytes, and the best test here is the hemoglobin, cellular hemoglobin content of reticulocytes, and below a certain threshold indicates decreased hemoglobinization of reticulocytes.

So here's an example of what happens to your hypochromic red blood cells measures, percent HYPOM on this instrument. So as I mentioned, it's using a laser light and it's detecting an incident light at two different angles, and one can target the cells

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

of interest here, and you can construct a histogram.

So you deplete iron stores. You get, you go under intense erythropoietic stimulation. You can develop a population of hypochromic red blood cells that can be measured in this test. Likewise, the reticulocyte hemoglobin content, this is an illustration of the histogram for this analyte.

The red here is indicated in the mature cells; the blue is a stain or dye indicating the reticulocytes, and you can see in an iron deficient subject on day zero, the reticulocytes have reduced hemoglobinization, as indicated by this line here.

If a subject then takes iron, and this is someone treated with oral iron, not intravenous iron. So it's a very rapid response. Once these reticulocytes incorporate that iron, then that can be detected as an increased reticulocyte

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

hemoglobin content.

You can see over time, of course, the reticulocytes diminish, as they should, and the mature red blood cells have incorporated the iron.

So those are analytes that can be used to measure iron deficiency. We decided to measure them as part of our RISE analysis, and in order to give you some background, I'm going to show you a study by Radtke that was published a couple of years ago. This was a cross-sectional study. It was fairly substantial in size, with over a thousand blood donors.

They looked at their biochemical indices of iron metabolism, as well as these ADVIA or red cell indices, and you can see that this is not longitudinal. This is retrospective. So they basically measured their ferritin and transferrin receptor levels. So this ratio was used in the study as the most sensitive indicator for iron

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

deficiency.

Males and females, males on top, females on bottom. They studied them. They looked at their retrospective number of donations, and this is a curve that I think we've seen before, in terms of the blood banking literature and what happens to blood donors over time as they donate. The more donations you get, the more ferritin-depleted.

The transferrin receptors do go up, and so the overall ratio, the log of this ratio, goes up over time.

You see this effect a little bit more pronounced in males than here in females, but it does go up. The trend is up in both. But you'll see there's a lot of scatter with both of these measurements. They measured red cell indices, in concert with the biochemical iron studies, and these, this is the kind of sensitivity and specificity they arrived at.

I want to show you first what I looked at here, the HYPOM, which I have

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

underlined here. They showed a sensitivity in detecting iron deficiency, defined as their most sensitive index, which is the log of transferrin over ferritin, of about 60 percent, with a specificity of 90 percent.

They also measured -- their CHr was about similar sensitivity and specificity. If they combined the two, maybe slightly better sensitivity with adequate specificity here. So this is basically the best they could show, with a combination of these two.

I'll show you just for reference here, the venous hemoglobin was very poor -- as we know, in terms of indicating early iron deficiency, only 18 percent sensitive. But it was specific. It is a late manifestation, so it is specific.

But the best test in their hands with this cutoff here, the hemoglobin, the ferritin level of 12 was about 60 percent sensitive, 99 percent specific. But they were able to improve to about 90 and 90, with a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

ferritin value of about 20.

Their conclusion here is this is a promising test from monitoring iron deficiency here or developing iron deficiency in blood donors. We, as I mentioned, also adopted this as part of the RISE study, and you've seen this on slides from yesterday.

We defined it as a very -- a level of iron that is so-called classic iron deficiency, where no one could argue that the donors were iron deficient at the most severe level, and we also defined a level of iron deficient erythropoiesis as the log of serum transferrin receptor over ferritin above 97 point fifth percentile, based on the male donors.

The reason for that is there's a lot of subclinical iron deficiency in female donors, as well even in first-time donors in the female population, particularly in the pre-menopausal population, and we wanted a very rigorous or firm definition for iron

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

deficiency.

In our studies, this ratio comes out to 2.07, and the other studies -- for example, in the study I just showed you was 2.5 -- they based their iron cutoff on a population of both men and women, whereas we use essentially a more rigorous definition.

So what was our ROC curve in our study? So this is the test performance for identification of IDE or serum transferrin greater than 2.07 in our RISE. This is from our enrollment database, and you can see here that the ROC curves do show that these are valuable or helpful in detecting iron deficiency to various strengths or various degrees of performance.

I'll just mention, HYPOM was actually the strongest, and that is in brown.

It's hard to see it here, but that's this curve here. The transferrin receptor was in red here, and this is the ferritin level. So you can see a very similar look to this as an

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

early iron deficiency study.

These studies can be helpful and red cell indices can be helpful. They can give useful information, but if you want to pick a test, the best test in our hands was the ferritin value.

Hemoglobin, I'm going to talk about that in terms of looking at sensitivity and specificity. You can also relate this as the Radtke study did, relate it to the actual sensitivity, specificity and the performance characteristics of the test. I'm showing you in blue the most sensitive index here, iron deficient erythropoiesis. This is an area under the curve, and I'm going to show you the more rigorous definition of severe iron or more severe definition of absent iron stores area under the curve, and this is grouped by rank from highest to lowest.

You can see HYPOM, in terms of -- if you were going to pick a red cell index, it had a pretty fair area under the curve in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

terms of its overall value, better than these other indices. MCV was actually the least helpful.

If we used a stricter definition of 12 for our definition of iron deficiency, we can see that these areas under the curve do increase, do shift over, and the P values, those are all obviously statistically significant.

So how does this relate to the numbers when we're assessing how to use these values? Well, the best we can do, in terms of these cutoffs -- so here are the cutoff values; here are the various tests that I've shown you there -- so HYPOM turned out to be the best, at about 77.

Most of these values that you see here, we could get to about 70 percent sensitivity, 70 percent specificity. CHr did not perform as well on the specificity score as it did in the Radtke study. We're not really sure why that is, but it's just what it

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

showed.

If you look at the MCV, with the standard 80 femtoliter cutoff here, it again was very -- it was not very sensitive, but very specific, no better than hemoglobin really. If we used a little higher cutoff, we could get the values up, but sensitivity suffered.

What I wanted to talk to you about was how well ferritin performed in our assay, and that is that the conventional classic definition, again, was not very sensitive, but was very specific. As we move up the scale, 26 seemed to be optimal in terms of very good sensitivity and pretty good specificity. If we start to go upwards on this, we start to lose specificity. It becomes less informative in terms of detecting iron deficiency in blood donors. So a ferritin of 26 looks like an optimal or an optimized value.

How did we do with venous hemoglobin? Well, these are all, at the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

enrollment we actually deferred subjects, based on finger stick. But we did get venous hemoglobin by ADVIA. So we could go back and look at how well venous hemoglobin performed.

As we know, there are big differences between what those tell us. This in fact tells us that the finger stick did allow some subjects with venous hemoglobins even below 12.5 to enter into the study.

But by changing this -- so here's the regulatory threshold of 12.5 grams per deciliter, and we can see in terms of the sensitivity very poor specificity in terms of detecting iron deficiency, based on IDE as the definition.

Very good, as you might expect, specificity. So if we move it up to 13, still not very good sensitivity. We're still getting a lot of donors with iron deficiency, who could donate with venous hemoglobins above 13, and likewise, the 13.5. It's only at this level, which of course is not a tenable level

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

in terms of a blood supply issue, that we would get decent sensitivity of venous hemoglobin.

So as we know and we've said repeatedly at this conference, venous hemoglobin really is a poor test for iron detection and should really -- should be separated from measurements of iron deficiency. It's not intended for that purpose. It's really intended to prevent anemia, detect and prevent severe anemia in blood donors.

I wanted to, in the last couple of slides, just talk to you about -- so our data's pointing toward the value of a ferritin as being the best value, and we can talk about whether we need a very specific value or a very sensitive value, and that data again depends a lot on what the clinical consequences of iron deficiency are in donors, and when those consequences appear.

But if we were to use a ferritin --

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

and some people have chosen to use gender-based ferritin values -- do we need two different values? Well, that is the tried and true laboratory method. There clearly are differences. So here's a population-based study of ferritin in males and females, and it's transferrin receptors shown at the top, and ferritin value is shown on the bottom, and they're grouped into females and males, females on top, males on bottom.

You could see transferrin receptors pretty even. There's no gender base. There's a slight difference here, but essentially there's no difference in transferrin receptor levels. So there's no gender basis for that.

There is clearly a gender basis for ferritin distribution, as we might expect. Females are lower than males. They're skewed to the left. Males look like they might be normally distributed or at least more evenly distributed. But a lot more women have low

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

ferritin levels, and that's a consequence of hemoglobin mass, sheer hemoglobin mass, as well as iron loss.

However, so you might say well, we should use different gender-based ferritin cutoffs. I'm going to show you two studies that argue against that point. This is the same study that I just showed you, and this is a population-based study. So basically -- and this is basically what I showed you on the first slide -- you could ignore this table.

Pre-menopausal women have 38 percent lower values for ferritin males, no surprise. However, post-menopausal women, there was no significant difference in ferritin, and then they also found in the study that 15 percent or so of their pre-menopausal women had low hemoglobin.

So they weren't really -- we weren't really detecting an iron-replete population. Their conclusion is that there's a high prevalence of iron deficiency among

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

pre-menopausal women, maybe higher than generally assumed, and other studies have pointed to this fact.

Another study really tells us perhaps what we should think about ferritin values, or at least the lower cutoff of ferritin between the two, and this is a study published in *Blood* a little over ten years ago. Transferrin receptor and the index identified -- and this was the title of the paper, "Identify Healthy Subjects With Subclinical Iron Deficits."

They gave iron to their subjects in the study, and so we have a pre-supplementation ferritin values, and I'm showing them encircled here. So men range between 14 and 188, and these were non-anemic subjects. So you know, equivalent or approximating a blood donor population.

The women, of course, had lower ferritin levels, as we see. After iron supplementation, really there's some

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

concordance, or at least with the lower levels. After supplementation, the women were actually higher than the pre-supplementation ferritin in men. But really there was no difference between these two levels.

So the reason we have gender-based ferritin differences is probably based on these studies, that there's a high incidence of subclinical iron deficiency. Once you're dealing with an iron-replete population, I think a single ferritin, as we've used in the RISE study, really makes a lot of sense.

This is just, explains their study.

They treated their males and females three months of iron, and all the subjects with IDE identified as this, an increased ratio in these women, 40 percent, corrected with supplemental iron.

So that points to using ferritin. Now here's the paper that appeared in *Transfusion*, I think, just last month, and I just wanted to talk about this very briefly.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

I think other speakers may talk about this later, but this is the, a study that shows a value or an apparent value in measuring ferritin levels in blood donors.

So this was a single center study in Switzerland. It was a longitudinal study over many years, over a decade, or '96 to 2009. 160,000 donations from 23,000 donors, small potatoes for some of our blood centers, and you can see this is a single center.

The serum ferritin was monitored or measured at each blood donation starting 2004.

They defined a very severe iron deficiency level here of 10 nanograms per mL, and any donor who had a ferritin at this level got medical counseling. Medical counseling consisted of: here are your options. Do you have a change of bowel habits, a very limited, what I gather from the paper, interview type, telephone interview type counseling session.

Here are your options. You can defer donation. You can take iron

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

supplements. You can see your doctor. The major results, and this is not a randomized trial, but it's quite, I think, interesting. Before and after 2004 when they implemented this policy, they found -- and these are just before and after comparisons.

So they found their baseline hemoglobin in the donors increased, in females more than males. About .26 grams per deciliter in females, .19 in males. Their number of anemic subjects decreased, using these European or WHO definition 12 grams, 13 grams, declined from 3.6 percent to 2.2 percent in females, and .7 to .5 percent in males.

They reduced their hemoglobin deferrals in females and males. They didn't report them separately, but they basically went down from -- they're going to be mostly females, of course. They went down from 2.8 to 1.9 percent.

They did see a reduced return rate,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

but one might expect that, based on counseling, based on going to their doctor and their doctor saying "Don't donate anymore. Your ferritin's 10, etcetera." But overall, this was considered a very positive experience, and at least it shows us kind of a concept that ferritin monitoring can have an impact, at least in this one single center.

So in summary, we've discussed a number of methods today. We've given you some insights on what might be the most helpful, in terms of monitoring iron in blood donors. We know that hemoglobin is not a useful measure, should be probably dissociated from that thought, and that RBC indices were not, did not hold up to our expectations, because there are just false-positives and false-negatives, and in terms of taking an actionable response, I think what we want is a real informative value.

I'll just say that in clinical hematology, ferritin values are the standard

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

of care. So they've been shown to be -- to impact iron deficiency, and to mean something in terms of monitoring that status in blood donors.

I just wanted to acknowledge all my colleagues in the RISE study, the REDS program, NHLBI and at the laboratories. Thank you.

(Applause.)

DR. GLYNN: Thank you, Joe. That was excellent. So any questions for Joe? We have time maybe for one. Everybody wants to go to break, so we'll take a break for -- oh, he's got one question.

DR. BUSCH: I was just wondering if you could extrapolate from the O'Meara study, if you had used the 26 instead of the 12, what would the consequences of that be --

DR. KISS: Right, okay. Good question, Mike. It really depends on what you think or what we find to be the clinical consequences, and the correlation or the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

severity of iron deficiency. I am persuaded by studies like the study that Dr. Illoh mentioned about iron supplementation, in improving fatigue.

I'll just tell you that study. What they did was they randomized non-anemic females with fatigue, and they scored the fatigue and they measured it carefully. They gave them IV iron, and then they, in a blinded fashion, recorded improvement in fatigue scores.

They selected as entry criteria donors less than 50, with a ferritin of less than 50, as their inclusion in the study. The one -- and then they analyzed the subsequent results. The group that had the benefit from the IV iron all had ferritins of less than 15.

That to me suggests that one needs a pretty good measure of severity for clinical consequences.

But what I don't know personally is how that level relates to brain function, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

I think we need more help to define how that relates to the non-anemic or non-hematologic consequences of iron deficiency. So -- but if I were to pick, I would say choose a very rigorous standard, probably the lower rather than the higher level. Thank you.

DR. GLYNN: All right. So we are going to take a break for about 15 minutes or so. We'll reconvene at about ten minutes after ten, or before.

(Whereupon, the above-entitled matter went off the record at 9:49 a.m. and resumed at 10:12 a.m.)

DR. GLYNN: All right. So our next speaker this morning is going to be Dr. Mast.

Dr. Mast directs the Basic Hematology research lab at the Blood Center of Wisconsin, Blood Research Institute, after serving as director of the Transfusion Medicine Service in Hematology and Coagulation Laboratories at the VA Medical Center in Memphis, Tennessee.

Dr. Mast has a strong interest in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

iron deficiency and iron metabolism, and he's actively involved in our research in this area, including currently leading a clinical trial of iron replacement in blood donors -- which hopefully Alan will talk to us a little bit about -- called "Strategies to Reduce Iron Deficiency" or STRIDE.

He's been an active participant in the REDS II and REDS III program. So the title of his talk today is "Iron Stores and Iron Deficiency in Blood Donors." Alan.

DR. MAST: Okay, good morning. Thank you, Simone. I would like to just present some of our data that we've found from several different studies studying blood donors, and hopefully you'll find it interesting. So I want to start just by reviewing what blood donation does to iron stores in a person. There's this simple graph.

It's typically said that males have about one gram of iron stored in their body,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

and females have about a quarter of that, or 250 milligrams. What's interesting, if you didn't know this, and it was mentioned earlier today, that one blood donation removes between 200 and 250 milligrams of iron. So in your average woman, the average blood donation will totally deplete all of her blood iron stores.

If you just do the math to calculate how much iron needs to be absorbed in different situations, based on normal iron loss, a male needs to absorb between a half and one milligram of iron each day. Females who are menstruating lose more blood each day, and they need to absorb between 1-1/2 to 2 milligrams of iron every day to replace their normal iron loss.

If you look at patients with hemochromatosis, these are patients that we mentioned earlier today. They absorb iron regardless of need, and end up getting total body iron overload that deposits in their heart and liver and can kill them. They

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

absorb around three milligrams, two and a half to three milligrams of iron each day.

Then Toby Simon in the 1980s did studies, where he looked at the maximum amount of iron that can be absorbed each day by the average individual -- it's around four milligrams a day. And if you take just the amount of iron, or you take a super-donor -- a super-donor is described as someone who donates every 56 days -- just doing the math, calculating how much iron they have to absorb every day, it's essentially totally maximal iron absorption. And depending on how you do the math, they might even have to be -- absorb more than what Toby calculated as the maximal iron absorption rate.

So this every-56-day donation interval really depletes people of their iron, and hope I can convince you of that. So this paper here, shown here, was the first baseline study from the REDS II RISE study, which has been mentioned many times so far today. Here

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

are the enrollment data.

This is just of the repeat donors or the regular donors in the study, those females that have donated two times or more in the past year, or males that have donated three times or less, more in the past 12 months.

When you do this absent iron stores, defined as ferritin less than 12, 16.4 percent of the males had ferritin less than 12. 27.1 percent of the females had ferritin less than 12. If you do the more sensitive indicator, the iron-deficient erythropoiesis, almost half of the men and two-thirds of the women have iron deficient erythropoiesis, just from this donation interval.

Then this paper is now published on line from the longitudinal study, the RISE data, and so we can look at longitudinal results of how iron is affected. What we found is that there's no effect of diet or menstrual status on iron deficiency in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

repeated blood donors.

However, there are significant predictors of iron deficiency. This is ferritin less than 12, including race, ethnicity, gender, age, use of iron supplements, and again, the center effect that we can't seem to get rid of, no matter what happens.

But the most significant predictors of iron deficiency were the number of red cell donations in the previous two years, and your time since your last donation. So when we donate blood, we lose a lot of iron, and that sort of swamps out all the other indicators of what happens, any other modulator, demographic modulator of our iron stores.

Here is the graph that shows in the Y axis the odds ratio for having a ferritin less than 12, and then on the X axis is the week since the last donation. The little -- it shows females in the blue diamonds, and males and females in the squares. We didn't

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

have enough data to calculate out the male results independently in this study.

So you can see at eight weeks, your odds for having a ferritin of less than 12 -- eight weeks after you donate blood -- are four to five times higher than when you haven't donated blood. This slowly drops over time to about 14 weeks. At 14 weeks, it seems to level out, and according to what Rich Cable tells me, is that that's -- the confidence interval is plus one at 14 weeks.

So it appears at least from these data that about 14 weeks to recover iron stores after you donate blood. If you look at their odds ratios based on their number of previous donations in the last two years, this is the data. The first time donor is set to an odds ratio of one by definition.

If you had less than four donations, it was between two and three. But then when you went between four and six, it raised dramatically to nine, and it stayed

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

there, sort of independent of donation intensity over time. So these two major findings from the RISE study, longitudinal study, that iron deficiency is related to the length of time since your previous donation and your donation intensity in the last two years, they're not really new, exciting findings, in my opinion.

Clement Finch published essentially the same results in 1977. Toby Simon published the same results in good studies in the 1980s. Yet the blood centers still haven't done anything to respond to this issue of making blood donors iron deficient, and one hypothesis that I have -- and I don't know if it's right -- is because they don't know how to do it, or we can't make it simple enough, or they don't want to really treat people.

I agree that if people don't go to donate blood because they want to go to their doctor, they go to their doctor because they want to go to their doctor. But I also think

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

that, you know, when they go to the blood center and donate blood, they're seeing people in white coats with stethoscopes and blood pressure cups and it's part of the medical establishment, and they expect to -- they should expect to get accurate information about what's happening to them, when they're going to donate blood.

So one of the things -- I'm going to go over this first. So iron deficiency, as we mentioned before, causes several things, and I think it can be bad. Iron deficiency, I think, poor iron deficiency is bad. Too much iron is bad, and you have to have people in the right balance. With blood donation, we make them too iron deficient, and you can make them have fatigue and decreased exercise capacity and decreased cognitive function.

Pica, which I think is very fascinating and clearly related to iron deficiency, results in restless leg syndrome, which some people have mentioned, and the RISE

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

study didn't turn out to be as correlated with iron deficiency as Pica did.

But I think part of the reason for that is because the symptoms for restless leg syndrome are so non-specific. I'm sure as I talk longer and longer, more and more people in the audience start to get restless leg syndrome.

(Laughter.)

DR. MAST: So one thing I do want to mention as sort of a little bit of a passion of mine is blood donation by 16 year-olds. Many teenagers have poor nutrition and are still undergoing cognitive development. They are not adults. They're still children, and any of you who have had a rebellious 16 year-old will have to agree with me on that point.

High school donations starting age 16, like when I wrote this slide was four to six times before they graduated possibly. But what I found from talking to our marketing

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

people and blood collecting people at our blood center in Wisconsin is, they are targeting the good high schools even more, and as long as the FDA allows them to say we can draw high school blood donors six times a year, just like any other donor, they're going to go to their best high schools and try and draw them.

Even though I have an M.D. and a Ph.D. in the study of iron for several years, I can't change their minds. So I need help. That's one of my controversial topics, to say my opinions. Okay. So I think it should be iron deficiency induced by blood donations, 16, and all donors should be a major concern of blood collection agencies. This beautiful girl here does not donate blood, because her dad won't let her.

Okay. So why haven't blood centers done this? So I was thinking -- we designed this R01. We have named it "Strategies to Reduce Iron Deficiency" or the STRIDE study.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Sort of one of the underlying bases for design of this study is to try to come up with -- not with ways to replace iron in blood donors, because we can do that -- I mean, just give them iron pills.

But what is the best ways or what are simple ways that are easily implemented, cost-effective ways that a blood center could do this, to try and reduce iron deficiency in their donors? So it's a multi-center study conducted at Blood Center of Wisconsin, at ITXM in Pittsburgh and then New England Red Cross. It's been funded through an R01 mechanism at NHLBI.

As I mentioned, the goal is to test methods for replacement of iron loss during blood donation that can be readily implemented in community blood centers.

Okay, and so one of the things that I wanted to mention is my thoughts about iron replacement or iron deficiency is: we should be focusing these on our regular blood donors.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Many of the donors come in once a year over twice a year, and aren't that frequent donors. I don't think iron deficiency in those donors is that big of a problem. I think it's when we start having them come in multiple times that is really where we need to be focusing our efforts.

I sort of view it as like setting up frequent flyer programs for airlines, trying to set up frequent donor programs for blood centers should be established, where we do different things to take care of these donors differently, because they're special donors to us and they provide us with a lot of blood and help us make a lot of money.

So what we've done for this study is divide us sort of into two groups, and study group one just going to receive a letter. So every donation, every time they come in, we're getting a ferritin value on these people, and based on their ferritin,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

they'll get -- okay.

So the first group, the first group just gets a letter. Thanks for donating no matter what, because they're the control group that gets treated like normal. So they'll get a thanks for donating letter and nothing else.

Then the Group 2 will get a letter, one of two letters based on what their ferritin value is.

One will be your iron status is normal, which we decided is greater than 26 for this study, just continue to donate. You're doing good. And the other one is your iron status is low, and we recommend you take one of two options. Either begin to take iron pills on your own, or delay your next donation for six months. Okay, so it's just -- so I think if that works, that's a pretty simple easy thing that a blood center can do. Do a ferritin value just on your frequent donors, which we could define in some way or another, and send them a letter and ask them to act on

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

their own, okay?

Study Group 2 is three additional groups of iron replacement, where actually we give them iron pills, and there's a placebo control study which the more I thought about it, it's very expensive to do a placebo control study. But I think it's going to be really important to make this study a lot better, and have the placebo group.

So this is, they'll be three groups, placebo 19 milligrams of iron. We chose 19 milligrams of iron because that's the dose of iron in a typical multivitamin. So I think that would be a pretty simple thing to do, to tell your blood donors to take multiple vitamins with iron.

It wouldn't cause too much legal hassles or anything. You wouldn't -- the blood center should be pretty comfortable telling their donors to do something like that. You're not treating the patient or doing all these things that people say the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

blood centers don't want to do.

Then there's some evidence that more iron than the 19 milligrams might be needed. So we also have a 38 milligram for iron dose in the study.

So the other thing, we had a meeting on Monday of the investigators. We all met here to talk about the study, and we had the preliminary data from the first 100 subjects that have been enrolled in the study, 200 subjects, first 200 subjects.

It seems like this is harder to recruit than RISE was, because we're putting interventions into these donors. But we are recruiting, definitely recruiting iron deficient subjects into the study. The average ferritin for the females so far is 12, and the average ferritin for the males is 24.

So we really are starting out, it seems like, with a solid iron depleted population, and we'll see how these interventions act to improve.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Another interesting thing that we have in this study is we have a survey, where we've done a pre -- we have a fatigue restless leg Pica syndrome survey, that we'll get at the beginning of the study and at the end of the study. So we'll be able to tell if any of these interventions are decreasing those symptoms, based on the results of the survey.

Okay. So that's -- I'm going to sort of switch gears here. That's the end of my discussion totally about iron, which you can summarize in blood donation, makes people iron deficient and we need to do something about it.

So I wanted to sort of change gears a little bit and review this paper that was mentioned yesterday by Bryan Spencer, where we looked a demographic correlates of low hemoglobin deferral in prospective whole blood donors.

This was tracking 715,000 donors over 24 months for low hemoglobin deferral,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

and then we developed a model to try and assess what causes low hemoglobin deferral.

I'm not trying -- I'm going back here for a reason. I'm not trying to go back to yesterday. But this is -- the odds for deferral is women have 11 times higher odds for deferral in this study than men, and blacks two to two and a half times more than whites. Hispanic women were similar to white women.

This is what was interesting to me.

Some of this data was shown yesterday, is that as we age, we have a much higher increase risk of deferral among the men. But with the women, it's not nearly as high, and the change. So this is dramatic change, right?

In the women, it's not that much. You can see menstruation and then post-menopausal. There's a small drop, but this is not very big at all, all right. Then you see this increase in aging that happens in women also.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So what was most interesting from these data, there was the odds for low hemoglobin deferral actually decreased with increasing donation intensity, and this has been mentioned, that we're selecting good donors.

If you look at just the women, which are the most likely to show this effect as they start out more iron-depleted, women with six donations in the previous 12 months have 0.45 odds for deferral, compared to women with one donation.

It doesn't make sense, right? It seems like the more they donate, the more likely they would be to be deferred. But it's the exact opposite. The more they donate, the less likely they are to be deferred. So what I'm very interested in is trying to understand the biochemical mechanism were selecting. My hypothesis, we're selecting for super-donors.

They're not the same as the rest of us. They have genetic, something different

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

about them that allows them to absorb iron and incorporate it into hemoglobin, to keep them from getting iron deficiency anemia.

So the characteristics of super-donors, these individuals donate whole blood every 56 days over a two year period, and they're losing lots of blood. So why don't they get iron deficiency anemia or have low hemoglobin deferral? We did a study of these donors at Blood Center Wisconsin, and I just enrolled, I think, 138 of them.

Half of them that I contacted replied and said they wanted to be in the study, just by one letter. So they're pretty dedicated people. So 60 percent had iron deficiency. So we're not protecting them from iron deficiency by being -- they're still getting iron deficient, okay.

They're not getting anemia, because that's all we're screening for is the hemoglobin, right? But they're still getting iron deficiency and many of them are not

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

taking, have no clue about the iron supplementation. Some of them did figure it out and are taking iron supplements. But many of them don't, and it's pretty clear at the Blood Center of Wisconsin, we need to do a better job of communicating that these donors that donate all the time would benefit from taking iron supplements.

We also, to try to get into sort of the genetic basis for what's going on with these donors, is we looked at their hepcidin levels. Now this graph here is their ferritin levels, and these are their hepcidins. A normal hepcidin by this assay, which was done by mass spec; we collaborated with the people at Eli Lilly to do these hepcidins on these donors, is between 10 and 15, right?

And most, over half of these donors had no detectable hepcidin by a very sensitive assay, which was mass spectroscopy to detect hepcidin.

So these people are really able to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

reduce their hepcidin and their plasma, and which you remember from the earlier talk, that turns your iron absorption totally on. So the faucet is totally on in these guys to absorb absolutely as much iron as they can. There's no inhibitor of it.

We don't know if these people are different from other donors. So you know, we don't know if you take another donor that's similarly iron deficient, is their hepcidin just as low as the super-donor. One hypothesis is these would be lower, but we haven't been able to do that study yet.

So other things that we looked at were genetic characteristics of these super-donors, and one obvious thing is these hemochromatosis mutations that cause hemochromatosis and this gene called HFE. There's a C280-2Y polymorphism and H63D polymorphism, which has more weakly been linked to iron overload disease. None of these donors were homozygous for the HFE

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

mutations.

There could be a selective bias in our study that I know there are some, because I've heard about them, donors that have a high risk for hemochromatosis. Their parents had it or they know they have it, and they just come and donate blood without telling anyone they have the disease and treat themselves. They wouldn't want to volunteer to be in this study, because we told them we were going to test for this.

But we looked at just the frequency of heterozygosity of these polymorphisms, and they're essentially the same as in normal population. There's no differences. There's enlarged studies of 99,000 people to determine the general incidences of polymorphisms in the population, and the super-donors are the same.

That's been collaborated and also shown in other independent studies, that high intensity donors, we don't select for people with propensity for hemochromatosis. We also

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

looked at the JAK-2 mutation, which is tyrosine kinase, that makes people get polycythemia vera, and none of them had this, and I was really glad, because I was thinking well, I don't want to have anyone positive for this mutation.

So we're not drawing blood from people that have polycythemia and don't know it. So what are these mutations? And it was mentioned earlier today is this TMPRSS-6 mutation, and TMPRSS-6 is a membrane-associated serine protease that degrades hemojuvelin. Hemojuvelin is a membrane, GPI anchor membrane protein that starts the signaling pathway that goes down and says how much hepcidin should be made.

So the more -- if you have mutations and hemojuvelin, you have hereditary juvenile hemochromatosis, its severe form. So TMPRSS-6 makes you have less hemojuvelin. You have to think through all this, every time, how it works.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So TMPRSS-6 degrades hemojuvelin, and so since if you don't have hemojuvelin, you have no hepcidin. It makes hepcidin be produced less, okay. So there's -- let me just summarize. TMPRSS-6 is important for regulating iron metabolism. What was shown, this is a plenary session in ASH, and there's a paper published out of Ernie Beutler's lab.

But when he was really sick when this paper came out, and his son, who just won the Nobel Prize, was the senior author on this paper. They found this cool mouse. They were just doing screens to look for different mice.

If you have a lot of money, you can just look for mice that have funky phenotypes, and then try and figure out what they are.

They found this mouse that had hair on his head but nowhere else. So they said well, let's figure out why is this doing, why does this mouse look like this? So it has -- that's the mouse, sorry. The mutation was in TMPRSS-6. This mouse doesn't make TMPRSS-6,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

okay, and it has severe iron deficiency.

So it has a -- TMPRSS-6 promotes hepcidin, I mean keeps hepcidin from being made. So if you don't have any TMPRSS-6, you have too much hepcidin and it's not -- they're not absorbing iron. What's interesting is if you give this mouse back iron, it won't grow back its hair. That's what we were talking about the other day, is if you keep your blood donors from being iron deficient, they won't go bald as quickly.

So the conclusion of the paper is that TMPRSS-6 is an essential component of a pathway that detects iron deficiency and blocks hepcidin production, permitting increased dietary iron absorption, which is exactly what I'm interested in. This is what the super-donors are doing. They're having increased iron absorption compared to other people.

And then after that basic science paper came up from the mouse, the next year,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

there's three -- this is just one of three papers that came out in *Nature Genetics*, doing this very large genome-wide association studies. I'm looking at hemoglobin iron parameters in normal individuals, and they came up with this one polymorphism that was highly or strongly correlated with hemoglobin levels in people.

So it's just a polymorphism somewhere near the active site of serine protease. If you look at where the amino acid chains, you could think well, it could regulate how well that protease recognizes its target substrates. So in the REDS III study as one of our Phase 1 studies or fast track studies, we're actually going to look at several, this polymorphism in a series of high intensity, and also the donors that are weak, poor donors, men that had readily deferred or likely to get deferred in the RISE study, okay.

So that's just one of the things

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

we're trying to do. I'd also like to do further studies doing total genome sequencing analyses of super-donors, to try and see if we could identify other polymorphisms that could help us identify why people absorb iron differently. Blood donors are a good way to study that, I think.

So in conclusions, it's clear blood donation causes iron deficiency, and programs are needed to assess iron status and prevent or treat it in blood donors. As things stand right now, I think ferritin testing is the best way to do this. We need to do ferritin testing on our frequent donors.

I want to know what my ferritin is.

Now that I know all this, then I can tell when I want to donate next. Donors are at different risk for hemoglobin deferral. Women can't donate as frequently as men, and in general, what I tell people is if you're a menstruating woman you can donate one or two times a year. Just don't even try to go more

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

than that.

We were sitting at our, just at the medical doctors' meeting at the Blood Center of Wisconsin, and we were sort of having a discussion about this, and we all sort of agreed that we came to the same conclusion.

That's what we tell our friends, if they're having a hard time donating blood, they should just donate once a year, twice a year. If you're a menstruating woman, you're not going to be able to do it too much more than that.

Then also I think it's important that older men cannot donate as frequently as younger men. My father-in-law has been an avid blood donor for life. It's like a personal thing. You just can't donate as much as you used to, and he doesn't want to accept it. But I think I finally convinced him. Just don't go as often.

I think the same thing. If you look at the donation deferral curves, you

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

know, I don't -- post-menopausal women. That's what I meant to say. Post-menopausal woman does not become a man, as far as her ability to donate. But an older man becomes like a woman.

So as you get older, they can't donate as much. They become -- so and this, so I'd say the same thing. And I also don't recommend that people over 65. My uncle was trying to donate double red cells in his 70's, and I said just don't do it anymore. So and he came back and told me. He said thanks for that recommendation. I feel a lot better.

So lots of people donate blood and they're all screened for anemia, and one of my most interesting research things are that blood donors are a rich source for study of anemia, the genetics of iron metabolism.

What we're doing is every day, I view it as we have this giant study going on, where we draw blood from about 95,000 people every day in the United States, regardless of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

their age or gender, and all we do is this little finger stick hemoglobin and qualify them, and then they can -- we can pull a whole bunch of iron out of them and we can follow what happens to them over time. So that's all I have. Thank you so much.

(Applause.)

DR. KLEINMAN: Alan, I have just a quick question about the STRIDE study. I may have missed this when you mentioned it. But the target population -- I assume the target population for enrollment is persons who have some, who are frequent donors or have some high likelihood of being --

DR. MAST: Right. The same as RISE. Women with two donations in the past year and men with three. Sorry. Mike.

DR. BUSCH: Yes. Alan, on the super-donors, I was a little disturbed. I hadn't appreciated before the significant proportion of what you were calling super-donors in your BCW study, were iron-depleted.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

I'm just curious, both with respect to the hemalogic and neurologic, you know, at some level these are people who just had high set points, and enabling them to donate frequently.

But they are becoming iron-depleted. Are they dropping their hemoglobins over time, their mean hemoglobins with serial donations, either in your study or in REDS? Have they --

DR. MAST: They do. I mean I didn't look at it in super-donors. I did it as a cross-sectional study of super-donors. It does drop over time obviously. I think that's pretty clear. Hemoglobin will drop over time.

DR. BUSCH: So though I like your hypothesis, I'm interested in the genetic correlates of enabling that. But to some extent, these people may just have high set points and be able to tolerate frequent donations. What about the CNS manifestations?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Have you looked in those super-donors at all, especially those who might develop, you know, anemia? Not anemia, but a declining hemoglobin, as to whether there's any symptomatic --

DR. MAST: We didn't do a survey of that in there. I'm really interested in Pica. I'm hoping we can use these donors to figure out what might be causing Pica.

DR. BUSCH: That's interesting. Richie.

DR. BENJAMIN: Alan, thank you. Clearly, the STRIDE studies are critically important, I think, and thank you for including the Red Cross in those studies, because I think they're going to be very important.

Just a couple of comments. I agree with you on your 16 year-old, 17 year-old daughter. I too have one of those. Very important we protect them. I wanted to make the point that the current proposed deferrals

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

that we're talking about, won't serve to do that, because we're only deferring the older donors, both on hemoglobin and on interdonation interval, and very few young donors.

In fact, it would have the opposite effect, because it would put more pressure on donation on young donors. So the current deferrals would backfire in terms of the young donors. The second point, your last slide where you had some recommendations on giving once or twice a year for females or older people, I guess doesn't really take into account the fact that we have selected -- those folks who have given that frequently have self-selected, to be able to do that.

We don't want to defer them, those folks. We want -- we might want to advise females to give less frequently up front. But the ones who can, can.

DR. MAST: Right. But the thing is the super-donors, I think, are pretty rare.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

DR. BENJAMIN: Well, we select them out, don't we?

DR. MAST: Right. They're a rare bird.

DR. BENJAMIN: Final comment. Again, one of your earlier slides on odds ratios, I think it was of iron deficiency, and it takes 18, 16 or 20 weeks to come back to baseline. Again, that's telling you something about a subpopulation that's iron deficient.

DR. MAST: I disagree. You've been saying that and I disagree with you. It's not. It's looking at taking this population and adjusting for everything we can, and saying okay, after adjusting for all these things, your odds are five times more than normal for having iron deficiency.

DR. BENJAMIN: Right. Maybe one percent for deferred and all of the sudden five percent are deferred. It's telling you about the deferred population, not about the 95 percent population that can give.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

DR. MAST: No, it's not. It's telling you about anyone who is in that population. It's telling you anyone that was in that study, what's their odds for having that happen to them.

DR. BENJAMIN: Right. But they actually want to look at the absolute numbers, rather than just the odds. The odds are -- it's a ratio.

DR. MAST: Well, the odds, the absolute numbers, I gave you at least percentages. For iron deficiency, there's a lot of it.

DR. BENJAMIN: Right. But you can't use the data of odds without showing the absolute numbers, because it leads to a bad conclusion, I think.

DR. MAST: Well, it's what's typically done in a lot of epidemiological studies. Okay, sorry.

DR. GLYNN: Unfortunately, we have to go on. So I'll ask you to reserve your

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

questions, put them on the little piece of paper, and then at the panel we can discuss those. In the publications, actually Rich, I should mention that in the publication you have the actual numbers supporting the odds ratios. So you can look at that.

Okay. In terms of our next speakers, it's Barbara, Barbara Bryant. She's an Associate Professor of Pathology at the University of Texas Medical Branch in Galveston, where she's the associate director of a blood bank, Director of the Coagulation Consultation Service, and the Director of the Clinical Pathology Residency Program.

Barbara's research endeavors include studies of hemoglobinopathies, investigation of iron depletion and deficiency of volunteer blood donors, and assuring optimal iron balance in blood donors with a routine use of iron replacement therapy.

She's also currently a co-principal investigator on the STRIDE study. So Barbara

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

is going to discuss iron stores and iron replacement in blood donors.

DR. BRYANT: Thank you, Simone, and I'd like to thank the organizers for inviting me to present today. I'm going to talk about our iron replacement protocol that we have at the NIH.

So just to give you a little bit of background, at the NIH, we see about 8 to 12 percent of whole blood donor visits in deferral for low finger stick hemoglobin. So we wanted to take a look at this. This was a protocol we started in 2006, and ran for 39 months.

The official name is "The Role of Oral Iron Replacement in the Routine Management of Blood Donors," but we affectionately called it the iron protocol for iron replacement or not. So this 39 month study, we had two groups of donors. They were either low hemoglobin donors or control donors.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

The low hemoglobin donors were those donors that presented to our donor room, and had a finger stick hemoglobin of less than 12.5 grams per deciliter on the day they presented. The control donors were donors who passed hemoglobin screening and were eligible to donate. They had to be not taking any iron replacement therapy.

The goal of the study was to analyze the cause of low finger stick hemoglobin, quantitate the prevalence of iron deficiency, study the long-term effect of blood donation on donors' hemoglobin levels and iron stores, evaluate the safety, practicality and efficacy of distributing oral iron replacement to blood donors, and determine the effect of the iron replacement therapy on the donor pool.

So when a donor was enrolled in the study after they signed informed consent, there was an additional health history screening that was done. We asked donors

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

information about have you ever been told that you were iron deficient? Have you ever taken iron? If so, what type, if you remember, and did you have any kind of ill effects in taking the iron?

Is there a family history of cancer? Do you have any GI or GU blood loss?

For women, we talked about their menstrual blood loss history, and also pregnancy history. Laboratory testing was performed, and we did CBCs using the automated analyzer in the Department of Laboratory Medicine.

We also did iron studies in lab medicine, which included ferritin, serum iron and percent saturation, as well as transferrin, and there were other tests that we ordered from time to time, just depending on the situation.

The iron that was used in our protocol was ferrous sulfate or ferrous gluconate, both 325 milligrams. The iron was issued from the blood bank. The sulfate had

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

65 milligrams of elemental iron, but the gluconate was just 38 milligrams of elemental iron.

So from the beginning, let me explain how we defined iron stores. We used ferritin. There's a lot of wonderful measurements out there, but bottom line, ferritin was available, it was cheap, and I could have the result that day or the next day.

So what we did was we used the normal ranges of ferritin at the NIH, which for women was 9 to 120, and for men was 18 to 370. So if you were below the normal range for ferritin, you were defined as iron deficient. In the low range of ferritin was depleted, and then we set a number for what we considered iron replete.

So for women, if your ferritin was less than 9, you were iron deficient. If it was between 9 and 19, we called you iron depleted, and we considered you iron replete

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

if your ferritin was 20 or greater. For men, any ferritin less than 18, you were considered iron deficient. Depleted was in the range of 18 to 29, and we considered a man iron replete if his ferritin was greater than or equal to 30.

So during the 39 month period, we had over 40,000 visits to the donor center by over 7,000 donors, and we enrolled in the study 1,236 low finger stick hemoglobin donors. This was greater than 90 percent of the donors who were deferred for low hemoglobin in our donor center. We also involved 400 control donors, so a ratio of about 3 to 1.

In the low finger stick hemoglobin donors, there were predominantly women, 89 percent, that had a mean finger stick hemoglobin of 11.8. There were 11 percent males in the low hemoglobin arm, and their finger stick hemoglobin was 11.9.

Of the 400 control donors, 37

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

percent were females with a finger stick hemoglobin of 13.7, and for men, predominantly male, with a finger stick hemoglobin of 14.9.

So here's a little bit more detail on the demographics.

Here's the low hemoglobin arm and the control arm, and as you can see, predominantly female in the low hemoglobin arm. The women were younger in the low hemoglobin arm, compared to the control group.

There were more men in the control group, but they were older in the low hemoglobin arm compared to the control.

African-Americans were more likely to be in the low hemoglobin group as compared to the control group. We also were able to determine from our computer database if they were first-time donors at the NIH. Our data went back to the 1960's at least.

So how many were first-time donors at the NIH? In the low hemoglobin group, it was more likely to be first-time NIH donors at

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

37 percent, versus 16 percent in the control group. We also looked at the number of prior donations, prior to being enrolled in the study, and for women it was 10 in the low hemoglobin group, 16 in the control group, and the men it was about the same one way or the other.

Actually, the successful donations in the previous year for the females in the low hemoglobin group were 1.3 and successful donations in the control group were 1.8 for females. So the studies revealed in the low hemoglobin groups, females were 30 percent iron-depleted, and 23 percent of the females were iron deficient.

Of interest here, the males of course, eight percent iron-depleted, but 53 percent iron deficient. So that makes sense.

By the time a man has a hemoglobin of less than 12.5 and was eligible to be in the low hemoglobin group, he was iron deficient. So he had iron deficiency anemia.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

In the control group, the big surprise was women in the control group, 29 percent were iron-depleted; ten percent were iron deficient. In the males in the control group, 18 percent iron-depleted, 21 percent iron deficient.

So even in the control group, these are the donors who are passing finger stick hemoglobin. 39 percent of those donors are iron-depleted or deficient.

We took a look at the finger stick hemoglobin levels and the iron status, as well as venous hemoglobin values in women and men, and for the women, we broke the categories into finger stick hemoglobin less than 11.5, the 11.5 to 11.9 range, 12 to 12.4, and then greater than or equal to 12.5. So this is my control arm.

We took a look as to whether they were iron deficient, depleted or replete in each of these categories. As you can see, starting here with the control group, this is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

the 39 percent that are deficient or depleted, but ten percent are deficient.

As you move into this category, which is the largest category of women donors that had low finger stick hemoglobins, 14 percent were iron deficient. Then you make the jump to 24 percent being iron deficient in the category of 11.5 to 11.9, and 40 percent here when it was less than 11.5.

So when you look at what is the best cutoff for hemoglobin values in women, we're using this 12.5. But in reality, there's not too much difference between ten percent versus fourteen percent, with a bigger jump down here at the 11.5 to 11.9. So you could argue that 12 grams per deciliter would be a good cutoff for women.

We also looked at menopausal state, thinking that that may play into this quite a bit. But in reality, it didn't. A lot of this interest in pre-menopausal women versus post-menopausal women, when we would take the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

history, women would report on post-menopausal, possibly surgically post-menopausal, and it would take years after they became post-menopausal to make up for some of the iron deficit that they had experienced for all those years of being pre-menopausal and having babies.

Now we did compare the venous hemoglobin, and what we asked here was was the venous hemoglobin greater than or equal to 12.5. In other words, have we been using venous hemoglobin determination by the analyzer in hematology? Would they have qualified for donation?

When you had greater than or equal to 12.5 by finger stick, 80 percent of the time that correlated. Now on the other hand, 20 percent of the time it didn't. But 80 percent. But this is very interesting. In the 12 to 12.4 range of the finger stick hemoglobin, 55 percent of the time the venous hemoglobin was greater than 12.5.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

So you could say in this category, it's like a flip of a coin, as to whether or not that finger stick hemoglobin that just deferred you was really accurate or not.

Now let's look at the men. This is finger stick hemoglobin levels in men and their iron status and venous hemoglobin, by different levels. We broke this down differently. Men less than 12.0 finger stick hemoglobin, 12 to 12.4, 12.5 to 12.9, 13 to 13.4 and greater than or equal to 13.5. So these three columns right here are my control arm.

So in the iron deficiency, you see that as you decrease the finger stick hemoglobin, of course the percent of donors that are iron deficient increase. So 19 to 26. A jump here to 56. However, the N was only 9 in this category here. It was pretty interesting, and then you have 46 and then 62.

So this would argue that maybe a little bit safer spot for men might be a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

cutoff hemoglobin of 13, because we all agree, 12.5 is below the normal range of hemoglobin for a male.

The venous hemoglobin again in this group showed pretty good correlation in the higher range, but as you got down closer to the 12 to 12.4, 69 percent of the CBCs drawn on the donors that had finger stick male donors with 12 to 12.4 gram hemoglobin, 69 percent of those were really greater than 12.5. But you still had this degree of iron deficiency.

Now I want to talk a minute about Pica and restless leg. There's been a lot of mention about well, are these patients, are these donors symptomatic, and they are symptomatic if you ask the right questions. In this study, we did ask donors about Pica and restless leg syndrome.

I have this picture here to remind me of the different things that donors talked about, when we asked them if they had cravings

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

for non-nutritive substances. The most common with iron deficiency is craving crushed ice. It's called pagophasia. It's quite common.

People actually hide that. They don't like to tell people they chew ice. Their family members know, and so sometimes the best question is how much crushed ice are you eating a day, and they'll answer it before they have a chance to sensor their answers. So quite a few of our donors that had Pica were eating crushed ice.

Some ate, I had one donor that ate frozen lettuce. Dirt, we actually had donors that admitted to eating dirt. Raw pasta. I had a school teacher who ate a box of chalk every time the kids went out to recess, and then starch. The ice was so interesting, these donors that were eating ice, that on the NIH campus, they could tell me where the best ice was in the building.

The funny thing was it was like behind the nursing station on the fifth floor.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

I mean they had to go looking for this, and they talked at length about how exquisite the ice was. I had one donor, when asked the question, she said well, she just ate popsicles, and it was summer so I didn't think much about it.

But I said well how many popsicles do you eat like in a week, and she said 106, because that is the largest container she could fit in her freezer from CostCo, and she could only go once a week.

As far as restless legs, we asked them if they had symptoms of restless leg syndrome, using the criteria that the neurologists use, and so we took both of these situations and asked about this on each return visit. Had this improved?

If so, at what point. Donors that were given iron that had Pica, saw a decreased interest in the non-nutritive substance, within about five to eight days. They just started losing interest, and it was completely

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

gone by 10 to 12 days.

Restless leg syndrome, we know that, you know, low iron stores can cause or exacerbate restless leg syndrome. As a matter of fact, the neurologists call anybody with a ferritin of less than 50 iron deficient and give iron to those patients with restless leg syndrome.

It took a little bit longer after we gave iron replacement. It took about six weeks before we saw any noticeable change, or the donor reported noticeable change in their symptoms. So we took a look at the association of finger stick hemoglobin levels with Pica and restless leg symptoms in women, and it became significant here when the hemoglobin was at less than 11.5.

Fifteen percent of the women with hemoglobin in this range reported Pica, and when we took a look at this by association with iron status, iron deficient, iron-depleted and iron replete in women, it was

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

significant in the iron deficient category for Pica, and the iron-depleted category of nine percent and 21 percent. Restless leg became significant in the iron deficient women at 18 percent.

We broke this out further, looking at the women in the low hemoglobin group, and again the Pica was significant at eight percent in the depleted category, and 21 percent in the deficient category in the low hemoglobin arm.

In the control arm, it was just seeing both the Pica and the restless leg were significant in the iron deficiency group. Now for men, the association of finger stick hemoglobin levels with Pica and restless leg, we saw that Pica was present in five percent - - significantly present in five percent of the men with a hemoglobin of 12 to 12.4 and 11 percent when they're less than 12.

So overall, when they weren't passing finger stick hemoglobin screenings,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

seven percent reported Pica. Restless leg was seen, though, just in the group that had hemoglobins less than 12, at 19 percent. So this was statistically significant.

When we looked at them by iron deficiency, depleted or replete, it was interesting. It didn't quite meet significance at all. This seemed to be more correlated with hemoglobin in men.

But when we broke it out by the hemoglobin groups, the low hemoglobin, it was just the restless leg at 21 percent in the iron deficient group, and in the control group we saw nothing that was statistically significant.

So donors in our protocol were given ferrous sulfate or ferrous gluconate, the 325 milligrams. They were instructed to take one tablet a day half an hour before bedtime with a half a glass of water.

People that take medication at night seem to have better compliance. Also,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

there's always a chance of a small, you know, intolerance, side effect, maybe a little nausea or something, and you'd sleep through it.

The tablets were issued in child-resistant blister packs, and I brought a pack to show, that they're child-resistant. The biggest complaint in this whole study was these things are hard to open. They're pretty much adult-resistant too. You have to take scissors or a knife after it.

Now in this study, we had 68 percent compliance, and we defined compliance as taking all the tablets as prescribed. Of course, the range was 0 to 100 percent. Initially in the study, 80 percent were given ferrous sulfate.

We had asked donors had you ever taken iron before, and if they said that they had and they were intolerant, we assumed they had been given sulfate, because it's the first line, and most doctors use ferrous sulfate

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

when they give iron.

So we took that 20 percent of donors and started them immediately on gluconate. We did not give them sulfate. But interestingly enough, in the donors that took the sulfate, 21 percent developed intolerance and were switched to gluconate. Of those that were switched to gluconate, four percent were intolerant to both the sulfate and the gluconate at the dosages we had.

Now in the group that was started on gluconate, the 20 percent that were intolerant -- reported intolerance to sulfate.

Nine percent had intolerance to gluconate. But overall in the study, only five percent were intolerant to both the sulfate and the gluconate, and of course the most common complaint was GI discomfort.

On this table, I have the development of adverse events, effects to iron replacement therapy.

Here's the ferrous sulfate group

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

and the ferrous gluconate group, and here, of course, are all the different things that people reported, most of which being GI, constipation, abdominal cramping, diarrhea, nausea, vomiting, bloating, indigestion, headache, metallic taste or sore mouth, rash or hives or other things, you know, foul flushing or foul-smelling urine, leg cramps, hyperactive bowel sounds.

You know, some of this may or may not even be due to these iron tablets. We had donors report, though, the severity rating of their symptoms. This was self-reported as severe, moderate and mild. Frequently, some of these could be quite profound.

Donors who had abdominal cramping would frequently wake up during the night, after that first dose of iron with abdominal cramping or nausea and vomiting. So donors that reported intolerance were offered a switch off the sulfate completely and go to gluconate.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So of the donors reporting adverse event, 17 percent on the sulfate and 47 percent on the gluconate, felt their symptoms were mild enough to continue, you know, just a little constipation. They'd drink a little extra water. Some people insisted that they wanted to stay on the sulfate. They liked it better.

Overall on the study, I had three percent of the donors in the low hemoglobin group that declined iron. I kept these donors on the protocol and just continued to follow them, because the hope was at some point, when they saw their lab results, they may change their mind and take iron.

Some didn't want to take iron because of just personal preference. They didn't want to take iron from -- they didn't want the blood bank giving them iron. I had some donors that needed kosher or vegetarian iron. Iron in the United States is not kosher. Our medications aren't. In Israel,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

all medications are kosher.

But in the United States, the tablets are coated. In this case, these are red. Sometimes they're green. That has animal byproducts in it, and it's not kosher.

So what I did do for the few donors that really wanted to take iron, I found a kosher iron supplement at a nearby store that they could buy, that had the same dosage of iron that we were giving in the study, and they were able to do that. Same thing with the strict vegetarians.

Then I had some donors that just refused, and I kept them in the study. That kind of accounts for some of our donors that took zero iron. So here's the effect of iron therapy in the low finger stick hemoglobin donors.

So this is kind of busy, but we have plotted the finger stick hemoglobin values, venous hemoglobin and ferritin values over a period of time by visit number. So

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

this is a low hemoglobin group. So their first visit, they had low finger stick hemoglobin, that put them in this arm of the study.

As you can see, here is the venous hemoglobin. But the finger stick hemoglobin, as they took the iron, went up and kind of maintained a nice level and stayed the same. When the donors returned, if they could pass finger stick hemoglobin, they could donate again. Now they were deferred for 60 days.

So as they continued to donate blood, they maintained a nice hemoglobin level taking iron. We see the same thing with the venous hemoglobin, and it's interesting in light of what was talked about yesterday, how the venous hemoglobin is higher than the finger stick hemoglobin at low ranges, but then it reverts to the opposite as you get back up into the normal range.

Also, the ferritin levels, we monitored that, and the ferritin levels went

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

up very nicely, and then just kind of maintained in this area. Nobody got a really high ferritin level on iron, because they were continuing to donate blood.

We also looked at the red cell distribution width and the MCV. So the MCVs, they tended to be low, and as they were on iron replacement, although they were continuing to donate blood, it stabilized, and the RDW initially went up, reflecting the replacement of iron, and then went back down in the normal range.

So donors on iron replacement had normalization of their laboratory parameters on iron, even though they were continuing to donate blood.

Now inherent in the study was a group of donors that I gave iron to, that were not iron depleted or deficient. So remember in the low hemoglobin group, they did the questionnaire. We did the labs, and I handed them iron at that point, not knowing if they

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

were iron deficient or depleted, or even replete.

So this is a group of donors that were iron replete. So they would not have really fallen into a category I would have given iron to, but we let them continue taking iron for the study to see what would happen. I wanted to know could I overdo it? Would there be a situation in which I could give too much iron?

So their hemoglobin -- and I have this broken out by apheresis male, apheresis female, whole blood male and whole blood female. I wanted to see if I saw some distinct patterns, and pretty much it looks the same. On the first visit, the finger stick hemoglobin was 11.8, and as they took the iron, even though they were considered iron replete, giving iron to these donors bumped their hemoglobin up one gram, and then it maintained.

So here's the ferritin levels. Did

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

I overdo it? So these were donors, look at their initial ferritins. They're in the normal ranges, and we gave them iron, and had them take it and continue to donate, and pretty much stayed level. You kind of absorb what you need and don't absorb the rest.

Now our control arm, remember these are donors not taking iron, that are passing finger stick hemoglobin. What happened to them? So as you can see, here's up here in the little Graph A, the ferritin level is plotted against the number of donations.

So when they were enrolled in the study, they had a nice ferritin level, and they're not receiving any iron, but they're continuing to donate. As you can see, it's a steady decline.

This graph shows donors that were identified on their first visit as being iron deficient. I did not treat any control donors with iron depletion. I waited until they were outright iron deficient, by our definitions,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

and gave iron. As you can see, then their ferritin goes up.

This is a group that we picked up on their second donation. They were okay on the first and they bogged down on the second and I gave iron and so forth on the third donation and on the fourth donation.

So control donors not receiving iron had a steady decrease in their ferritin level. So as far as safety, this was of course a big concern. I didn't want to mask an underlying condition. I didn't want to, you know, cause any donor harm. One of the things that we did is we spent a lot of time reviewing these health history screening information, to see if we could find something.

Sure enough, it became obvious very quickly. We had eight donors report dark blood in their stools or dark tarry stools, and they were sent to their physicians. Seven of these reported that, and they had

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

gastritis. There was one donor who we gave iron to that continued to have a decreased ferritin and hemoglobin, and that was picked up that way. So eight cases of GI bleeding.

We had one control donor that when we took a look at the CBC, he had 1.4 million platelets. So he had essential thrombocythemia. When we spoke to his physician, the physician said yes, that's really interesting. It looks like we've run CBCs for the last two years and it had been present for two years, but the doctor hadn't noticed it.

We had two cases of vitamin B12 deficiency. This is certainly not something I was looking for. But as you take donors and you give them iron and you correct that iron deficiency, some donors, these two donors, their MCVs went sky high. They went to 103, 104 and we ran for latent B12. So we were able to identify B12 deficiency.

We had one very unusual case of a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

woman who had been a regular blood donor. She's a platelet donor. She came in, she didn't pass hemoglobin screening. She had never failed hemoglobin screening before. We were a little curious. Her MCV was low, her RDW was normal. We ran hemoglobin electrophoresis. Her hemoglobin A2 was over four, which would make you think of beta thalassemia possibly.

But this just didn't seem to make sense. So I talked to her and she insisted she was not from, family of origin was not from any region in which thalassemia is associated, and we had her come back in, and from about ten feet away, when she walked in the door, you could see the goiter in her neck.

She had hyperthyroidism. By the time we had seen her, this was three days after she had originally presented, she was mildly tachycardic, had Palmar erythema, had a bruit, and we got her to see a physician that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

afternoon. The physician got called away on emergency and that night, she ended up in emergency room. But she had all the labs. We had run thyroid studies and provided her the labs.

We picked up one case of Raynaud's, five cases of diabetes, certainly something I wasn't trying to pick up. But in the course of doing this, if a donor told me I have never been able to donate blood, no one in my family has donated blood, and I would sometimes run hemoglobin electrophoresis.

In these five cases, we picked up increased P2 spike on the HPLC, and that increased spike is associated with the hemoglobin alc. So we were able to diagnose these five cases. Three donors knew that they had it, but for two donors, it was a new diagnosis.

We had one case of early myelodysplastic syndrome that we picked up, one case of hematuria, a case of substance

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

abuse, and numerous hemoglobinopathies were found. Laboratory data confirmed severe iron deficiency in two of our donors with gastric bypass surgery greater than five years earlier. A lot of these patients know that they have to take B12, but they are not being followed for iron.

We had one donor that had just a profound nose bleed, and had lost a bunch of blood, and we had a donor who had had a complete gastrectomy 40 years earlier for gastric ulcers. None of the donors in our study were found to have ferritin or transferrin saturation levels suggestive of hereditary hemochromatosis, and there were no malignancies reported or detected.

Now, the long-term donor center operational effects, we looked at the interval between visits in the low hemoglobin group and in our control group, and for the women in the low hemoglobin group, it was 92 days, and for the men, 76.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

In the control, it was 94 days for females and 81 for males. So overall in the study, the interval between visits was 87 days.

We had hoped to see a reduction in donor deferrals, and this was not sustained, because we found that donors came more frequently when they were on the iron tablets.

It's almost like having a visual reminder every day, how many more red tablets do I have to go until I can go back to donate?

So we found, however, that the average productive donor visit, per donor per year, was during the 39 month study, for the whole donor population, was 1.3, 1.1 for females and 1.6. But those that were enrolled in the iron study, both the control and low hemoglobin arms, it was 1.9 for the study population, 1.5 for females and 2.8 for males.

So, although the donors in the iron protocol had higher deferral rates, they returned to the blood bank more often to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

attempt donations, resulting in a 46 percent increase in productive visits per donor per year, compared to the general donor population. Thus, the donors on iron donated more units of whole blood per year than the general donor population.

So as far as study costs, the intangible costs, this is pretty cheap. Iron's super cheap. Overall, it was less than \$12 a visit, and we were doing all this laboratory testing. So it was, you know, \$10 for testing, \$1.40 for the iron tablets.

But the biggest cost, of course, was physician oversight, and we had health professionals helping with the medical history screening, collecting and ordering the labs, promoting compliance and assessing intolerance, and we had to have someone maintain a database.

So in summary, blood centers are confronted with the ongoing challenges of iron deficiency in blood donors, both the pre-

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

existing, especially in females, and the resulting iron deficiencies. Altruistic donors come to give the gift of life, and this is an opportunity for blood centers to give something back.

Iron replacement therapy is a cheap, safe, and effective method of preventing iron deficiency in blood donors. It's got advantages for the donor. It increases your successful donor visits, and it enhances donor well-being by preventing symptomatic iron depletion or deficiency. So you have overall donor satisfaction.

The advantages to the donor center is it results in more productive donor visits, which means more blood, and it improves donor retention. It's always cheaper to retain a donor than to have to recruit a new one. So it's a win-win situation. So we have the issue. We have the responsibility to balance these issues, to maintain suitable blood supply and ensure donor health.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So based on this study, what would we recommend? We'd recommend administering a two month supply of oral iron to all donors with hemoglobin less than 12.5. If the male has had a previous blood donation, we would only refer the male to the primary care physician if he doesn't respond to the iron in 60 days.

If he's a first-time male donor and he's showing up with a hemoglobin less than 12.5, he needs to be referred to a physician.

Males with a hemoglobin of less than 12 or females with hemoglobin less than 10, need to be referred to a primary care physician.

You can go further though, based on the study and the safety profile that we had, that the evidence-based recommendation is you could safely administer a two month supply of oral iron tablets, which is sufficient to replace the iron loss in one unit of whole blood to all whole blood donors.

Donors give a unit of blood, it's

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

240 milligrams of iron. If you take one of these tablets, and this is the ferrous sulfate, take one of these tablets every day for 60 days, and you absorb about six percent, you're going to absorb about 238 milligrams of iron.

So it's a tradeoff. They give us iron, we give them iron back. If you're uncomfortable about giving iron to somebody because you're afraid you may miss someone that has hemochromatosis, you could do a single ferritin level to verify a non-hemochromatosis status.

So I'd like to thank everyone that I worked with at the NIH, Susan Leitman. You Ying Yao is our database coordinator. We had two nurses that worked quite a bit with that protocol, Julie Hopkins and Sarah Arceo. Of course, Harvey Klein, all of the blood bank staff at the NIH, as well as the staff in Laboratory Medicine and our blood donors. Thank you.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

(Applause.)

DR. GLYNN: Thank you, Barbara. I think actually we'll hold on questions, because we're running a little late. And again, if you can put your questions on the little cards, and then we'll discuss them at the panel.

So our next speaker or last speaker for the morning session is Dr. Keller. Dr. Keller is currently the National Donor and Product Safety Specialist for the Australian Red Cross Blood Service. After being Director of the Western Australian Blood Transfusion Service since 1984, he has a major interest in multiple publications in transfusion-transmissible diseases and the safety of the blood supply.

So today he'll talk to us about the Effectiveness of Post-Donation Short-Term Iron Replacement in Female Whole Blood Donors.

DR. KELLER: Thank you very much for that introduction, and for the opportunity

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

to speak today. I'm going to talk about this trial, but I'm going to give you a little background beforehand, to orientate you to how we ended up doing this trial.

So I was going to talk a little bit about whole blood donation and iron balance, but there's been so much so I'm going to skip through that quickly. I'm going to talk about a study of ferritin levels of blood donors in 2004, which led to practice changes, largely in -- as a result of communication with our regulator, who was increasingly concerned about our hemoglobin threshold levels and the prevalence of iron deficiency and the chance of iron deficiency in the population.

Then about the trial that we've set up and some mixed steps, now that the trial is completed. This would seem to offer about iron storage. But the interesting thing about this graph, which came from Cook, here that males really don't reach their full storage level of iron up until the age of 25, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

females really only start increasing after the age of 45, when they're becoming post, well after the menopause.

To give you the background, the current interdonation interval is 12 weeks. We collect 470 mls of blood, with about 30 to 40 mls of samples on top of that. As you've heard, somewhere about 220 milligrams of iron, and we absorb about two to four milligrams a day. Now we've talked a lot about this, heard a whole lot about this already.

Is the interval sufficient? Well, maybe not, with the data that we've heard yesterday. It may take longer to replace iron stores for that supplementation. Donors are susceptible to negative iron balance from frequent donation, and the additional iron losses increase requirements for iron in used donors, particularly reduced dietary iron intake and in vegans and vegetarians, and now anorexics and bulimics in our young population, that this is a real problem, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

impaired iron absorption, for example, undiagnosed celiac disease.

This is just a nice graph showing what we saw yesterday, progressive iron depletion. First, you have storage iron and then of transport and functional iron, and some examples of laboratory profiles which I won't go into.

We've heard all about the side effects, so I won't talk about that. But in Australia, a lot of hemoglobins deferrals account for about 16 percent of all deferrals.

About 75 percent of those are due to iron deficiency, and 60 percent of those are in pre-menopause females. So we have a significant problems with iron deficiency anemia.

And donors who are deferred, and I think this is probably a general phenomena, or less likely to return, we have a study showing this, than non-deferred donors, and when they do come back, they give far less donations

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

than their non-deferred colleagues.

We have, I think it's been pointed out, we have a duty of care to our donors, that they come in voluntary to give us a gift.

I think I agree with the previous speakers, that in many cases, we're actually causing harm to them.

So again, in Australia, who contributes to the blood supply? Well this shows in the middle group there, the 26 to 50 year-olds contribute most of the blood supply.

Females slightly predominate in the less than 25's, and males here in the over 50's.

The frequency of whole blood donation by gender here. This is in -- sorry, I'm just lost here for a moment. These are the females and males, the total number of donations at the end, and the frequency of donation tails off. Mostly one or two donations, around about 70 percent, 70 to 75 percent give one or two donations, and 25 percent, three or more donations.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Right. So in conjunction with, or after dialogue with the regulator, we undertook this study in 2004, and the aim was to determine the ferritin status of eligible whole blood donors, stratified by gender and age. We chose a ferritin level of less than 12 to define high deficiency, and we didn't distinguish between genders.

We chose whole blood donors who met our guidelines of the day, and we had lower thresholds than almost the rest of the world at that time, 11.5 grams per dL, the females, and 12.5 for males. We recruited just over 3,000 into the study.

The prevalence of iron deficiency at that time was a big surprise to us. In females, in various age groups, it was 20 percent or more, and greater in pre-menopausal women, and also a significant level of iron deficiency in men as well, with an overall rate of about six percent in men.

In donation frequency, as we've

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

seen from previous speakers, increasing with increasing donation rate in all groups in fact, but much less so in males. But I think this is the important level here of all donations. 37 percent were iron deficient for females.

This is just a table of some of the studies that have, that have been done of iron deficiency in female donors, in both new and return donors. This is 23 percent. We had very few new donors in this group. So I think the return donors was about 23.9. But they were all around about 30 percent or more.

There are many differences in here, in cohorts, in deferral periods, in nutritional levels, et cetera. So you can't really compare them. But they're an interesting illustration.

So what did we after that ferritin study? Well, we increased the minimum hemoglobin thresholds over a two year period. We did it in two successive stages. The first

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

stage was 100 females and 115 to 118, and then 120, where there was some push due to the Council of Europe thresholds, because in Australia are mandated to the Council of Europe guide to the preparation, use, and quality assurance of blood products which has these levels, but we resisted that and we went to the UK levels at the time, and very soon after this the UK, of course, changed to the Council of Europe. So we're still alone, I think.

We introduce intensified dietary advice, and this is before we knew that diet probably doesn't have a great effect on preventing iron deficiency. We introduced limited ferritin testing for all those who had hemoglobin below the minimum thresholds.

If you had a 20 or two gram per deciliter drop between successive donations, or if the blood count parameters, particularly in apheresis donors, suggested that they might be an iron deficiency, and these were the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

ranges for ferritin that we used at the time.

We defer, our current policy is to defer people for iron deficiency and iron deficiency anemia, and we send them off to their GP for diagnosis and treatment and management.

Since then, we've also introduced saline replacement for plasma pheresis. So our apheresis donors, plasma pheresis donors, in particular, are losing less red cells, and we have a very good plasma pheresis program, close to 300,000 units a year, out of a total of 1.3 million donations.

So we have were considering post-donation and replacement at this time, but the literature was really sparse on the actual clinical effects of iron deficiency, other than anemia. We had trouble with the selection and availability of a suitable dose preparation in Australia.

We have ferrous sulfate and ferrous gluconate, but they do have high

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

gastrointestinal side effects, and we were looking for something, too, that was perhaps safer. We don't have the stringent blister pack facilities that you do in the USA.

So we were worried about safety. We were worried about the risk of exacerbating undiagnosed iron overload without doing ferritin levels, of masking gastrointestinal pathology, what would donor uptake and compliance be like, and international benchmarking. There wasn't really much good data out there about supplementation.

In overcoming those hurdles, we concentrated on this group of pre-menopausal donors, because there are almost 236,000 donations coming from this group. We thought the gastrointestinal pathology would be less of a problem in this group, and that we might actually increase the donation rate if we could correct some of this iron deficiency, which are unidentified. So in Dr. Bryant's words, a win-win, a win-win situation.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

We also became aware of the cognitive decline in young women, which was corrected by iron supplementation, in a couple of studies that we became aware of, and our board became aware of that and our executive, and we were extremely concerned, because we collect from 16 year-old high school students who are doing exams, and we're just worried about the consequences, but not only for the donor but in terms of later litigation as well.

So we saw, did suitable preparation, which was the carbonyl iron is not available in Australia, so we had to especially have this made up, 45 milligrams of carbonyl iron, and we chose this dose from a publication of Dr. Newman in 2006. He said that 40 milligrams over an eight-week period would restore iron levels.

This had a much wider safety margin. I think mice can take up to ten grams without falling over, and humans similarly.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

It was reported to be efficacious and well-tolerated, and as I said, we chose the group because of reduced risk of GI pathology and less risk of exacerbating hemochromatosis.

So this was -- we then did a randomized double blind placebo-controlled trial, to see if 45 milligrams of carbonyl iron over eight weeks could ameliorate the iron loss from whole blood donation in that pre-menopausal group.

Of course, we got ethics approval, informed consent from our subjects. They were all notified of ferritin results once we'd done them at the end of the study, and they were referred, those with iron deficiencies were referred to their family physician for treatment.

Females 18 to 45 years, they had to have a history of successful blood donation the previous two years. They had to be eligible, and undergo successful blood donation on Visit 1, not be pregnant. Indeed,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

they had to be taking precautions against pregnancy, and willing to come back in the 12 weeks for the follow-up visit.

We had a lot of exclusions, because we didn't want a whole lot of confounding factors. So anyone with hemochromatosis or red cell abnormalities was excluded, as was GI pathology. Any regular medications known to interact with iron supplementation, concomitant iron supplementation.

There are many products in Australia which have less than five milligrams of iron, which are pretty useless. But they're in multivitamin preparations and people do take them. But we consider that that would have an insignificant effect. And allergies are dealt with within the study medication.

We were originally told that we would be incorporated in the placebos, so we excluded all people with asthma, and then they decided not to include it. So as I say, we

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

did have a lot of exclusions.

The primary efficacy end points were ferritin of less than 15 micrograms per liter. We chose that level, rather than 12 based on I suppose international studies or international evidence.

We've seen people have referred to that today, and body iron reserves, using the soluble transferrin receptor and serum ferritin values using this formula of Cook's, although I'm not reporting that today, because that analysis is still proceeding.

The second end points were eligible to donate at the 12 week visit, based on the capillary hemoglobin, instance of gastrointestinal complaints and attitudes towards supplementation. So we recruited, I think, about 1,300 people. About 900 were excluded, if they didn't want to participate or they had some exclusion criteria.

They were randomized in block randomization protocol. They were given the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

study medication with instructions to take one tablet half an hour before bed on an empty stomach. They had a diary count. They were followed up by telephone, to make sure that they were complying and they were given access to the study team 24 hours a day if they had any concerns.

At Visit 2, they reported compliance, brought their diaries in, and had samples for ferritin serum transferrin receptor, the same as at the first visit, and most of them gave a donation. So this is what it looked like, and it's a very busy slide. But we've got enrollment up here, allocation.

We ended up with 282 randomized participants, 141 in each of the two groups. We had two dropouts here, and a small number of dropouts in both groups. So we ended up with 129 in the carbonyl iron group, and 128 in the placebo group. But we had allowed for ten percent dropout. 262 was based on the power of 85 percent, with a significance of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

oh-point naught 5.

So the analysis. Just to tell you, the main efficacy analyses were conducted on the efficacy population. The safety analysis, on those who had taken at least one dose of the study medication, sub-group analyses were performed, based iron deficiency status at baseline. I'll show you these.

We didn't do sensitivity analysis, because we had a control expert group who were advising us, who said that we really didn't need to do this, given the very low dropout rate. So these were the baseline parameters, and I won't go through them. But they're very well matched groups.

Treatment compliance. Now this shows, in terms of compliance, that there was no significant difference. In terms of the main analysis, first of all, the median ferritin, we did median ferritin because the ferritins were not normally distributed, and the long ferritins were not normally

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

distributed either. So we had to use non-parametric tests.

But we can see here in the carbonyl, we only looked at this data and we looked at Week 12, but you can see here that that carbonyl iron group had a significantly higher median ferritin than the placebo group at Week 12, and the subgroup analysis, looking at those who were not iron deficient here and those that were iron deficient at baseline, both of those groups had significant higher, significantly higher median ferritin values.

This is the analysis of the iron deficiency status at Week 12. So the percent of iron deficient people at Week 12 is much higher in the placebo group than the carbonyl iron group and highly significant. So we can say that the carbonyl iron does prevent people becoming, some people becoming iron deficient in that group, and again the subgroup analysis shows that both in those who are not iron deficient at baseline and those who were iron

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

deficient at baseline, that we've still got a significant difference in those who are iron deficient at 12 weeks.

Hemoglobin high levels is capillary hemoglobin levels, a significantly increased hemoglobin level. I think it became a globin level at 12 weeks. In the Subgroup analysis, if you were not iron deficient at baseline, it didn't reach, there was no difference.

We didn't reach any significance. But if you were iron deficient, your hemoglobin level was significantly elevated if you'd been on carbonyl iron. This is unfortunately that increased hemoglobin didn't translate into increased eligibility at donation. The differences were not significant. There was a trend here, and we think if it had been more than one cycle, or they had had a longer dose period, that it may have made a difference.

So in summary, we can say that 45 milligrams of carbonyl iron compared with

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

placebo in this particular group, leads to a higher median ferritin value, less iron deficiency at a 12 week period, and a higher capillary in the globin as well.

Now gastrointestinal side effects we looked at, and we haven't done significant levels on these. But they were a high number of adverse effects in the carbonyl iron group.

The yellow are mild effects. So most of the effects were mild. The red is severe. There are only two severe, and if you take out this group here of darkened bowel motions, which does occur, the groups look very similar indeed.

We asked them at the end, were they prepared to continue taking iron as carbonyl iron in further donations, and 87 percent said that they would. So a pretty good compliance rate, which was better than the placebo. So again, the summary, post-donation course of 45 milligrams of carbonyl iron in that pre-menopausal blood group, effective in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

ameliorating iron loss associated with whole blood donation.

Effective in reducing the proportion of iron-deficient donors, well-tolerated and quite high donor approval. So the limitations with the restricted eligibility criteria, just a very short course, an eight-week course over a single cycle.

The implementation challenges, because we had 1.3 million donations a year, we've got 100 centers, so it's spread out over thousands of miles, and what we really need to do now is an effectiveness study, to see if we can wheel this out into the general community.

So we've set up an Iron Task Force, and some of the things that we're doing and we're trying to integrate this with ferritin screening, with tailored donation intervals, as we discussed yesterday, and doing some work with eProgesa, which is our national blood management system, to see if it can

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

incorporate a module to deal with, you know, 1.3 million donations a year, to predict generally donor uptake and compliance.

We still don't have carbonyl iron in Australia. We are negotiating with the company to get it registered there. But we're also looking at another preparation called iron polymaltose, which in the literature at least, it's extremely well-absorbed, there's very low side effects, and looks a very good preparation. It's available intravenously, but it's about to become available orally in Australia.

Cost-benefit analysis. As well, we want to look at the long-term impact on deferrals and donor retention, and the long-term consequences of iron replacement. So we're doing -- these are the objectives of the Iron Task Force, which I think are fairly -- and one of the things that we want to do is develop educational resources for staff, health professionals and donors, and actually

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

putting something on the website so that when we send people to the general practitioners, that they will investigate appropriately.

I think the British Society for Haematology has recently published some guidelines that include investigation of donors with iron deficiency, and I think we either need to adopt those or develop something ourselves in conjunction with the gastroenterologists and hematologists, that will stop everybody, when you refer them off to a specialist, everybody being scoped, upper and lower scoped, and that has a real risk of adverse events.

1 in 1,000 colonoscopies, in Australia anyway, are complicated by a bowel perforation. So it's not an inconsequential thing to do in a reasonably healthy person. So we're also looking at our consent process, to make sure that donors really understand what iron deficiency is all about and what they need to do.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

We're trying to deal with ferritin screening and how we -- because if we refer everybody often, we do a ferritin study onto the general practitioner, we will abolish the Australian blood supply overnight, I think. We're looking again at minimum thresholds, but I don't think we're going to anything there. It's a poor relationship between hemoglobin and diet, and developing a literature database as well.

So with that, I'd just like to acknowledge all these, particularly Joe Speedy and Denese Marks, who have done a huge amount to get that study going. Our transfusion medicine specialists, Kathryn Robinson and Phil Mondy and Magda Teague, and the study, the people who actually did the study, nurses and doctors. So, and the Australian government, who extended this research grant.

So thank you very much.

(Applause.)

DR. KELLER: Shall I stay here?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

DR. GLYNN: We can take one or two questions, if you want.

DR. KLEINMAN: Steve Kleinman, AABB. Tony, that was quite interesting. So just to follow up on your last couple of slides, about plans for the future. So you had a lot of potential strategies and things that need to be worked out. But I'm assuming that the decision has been made to do something.

I mean, in other words, whether you can actually do ferritin testing or administer iron routinely, I guess you still have to work out. But you are going to work out a plan and take some action, and not leave things as they are; is that correct-seeming?

DR. KELLER: Yes. I think we've got enough evidence. We just can't ignore this. We can't ignore this anymore, and our executive, in setting up the task force, is expecting a strategy which will progressively deal with this problem. It won't happen

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

overnight and it will be wheeled out in slices.

DR. KLEINMAN: Of course, yes.

DR. KELLER: But yes, we're determined to do something.

DR. BUSCH: Tony, Michael here. In your randomized trial, I can kind of understand extra precautions, but your comment about requiring that women both not be pregnant and be on contraceptive, it sounded as if -- is that something that you would consider necessary in order to prescribe?

DR. KELLER: No. The reason for that, this was a trial medication in Australia. Although it's available overseas, we had to treat it as a new drug, and until it's registered in Australia. So no, we wouldn't exclude people in the future. In fact, it would probably be quite beneficial for people who wanted to become pregnant.

DR. GLYNN: Thank you, Dr. Keller.

So we are going to break for lunch for about

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

an hour. So we need to be back and we will start at ten minutes before 1:00. Thanks.

(Whereupon, the above-entitled matter went off the record at 11:46 a.m. and resumed at 12:51 p.m.)

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

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

12:51 p.m.

DR. GLYNN: All right. So we're going to get started the afternoon session. The first presentation of the afternoon is going to be by Doctors Busch, Custer, and Kamel of Blood Systems, and it's entitled "Blood Donor Hemoglobin and Iron, Research -- on Policy." Dr. Busch will start and discuss comparative effectiveness research and efficacy, versus effectiveness.

This will then be followed by a presentation by Brian Custer, on the characteristics of blood donors at Blood Systems, and then Dr. Kamel will talk to us about the potential comparative effectiveness studies that could be considered to evaluate different strategies that should mitigate iron depletion deficiency in blood donors. All of that in 23 minutes.

DR. BUSCH: Thank you Simone, and thank you Rick, for this conference. It's

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

really been superb, and yes. What we're going to do today is to present a fair bit of data, and then present some strategies that we've considered as possible interventions, if you will, to reduce the problem of anemia and iron depletion.

The approach that we've developed is really following up on the lead that Simone made us aware of in a workshop she convened about six months ago, related to the process or the concept of comparative effectiveness research.

This is kind of a new concept, at least to me, but a field of research that's kind of evolved over the last ten years, and has really been prioritized by the Institute of Medicine and other groups as a more meaningful and cost-effective way to get generalizable conclusions by generation and synthesis of evidence, looking at broad questions of the effectiveness of alternative methods in the context of all kinds of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

different clinical interventions.

It's really designed to assist, in a great sense, policymakers to make informed decisions, both that individual and most important at the large population level. A couple of other terms again from the Institute of Medicine report.

This is also called "clinical effectiveness research" or "patient-centered research," and it's really designed to assess which treatment works best under a whole variety of conditions and defines, you know, specifics as to what circumstances a particular intervention screening, diagnostic treatment modality would be most useful.

It's the concept of effectiveness compared to efficacy, and I'll just show a couple of slide in a moment, contrasting those two concepts. Again, it's usually looking at multiple possible alternative approaches to addressing a situation. One of them can be kind of the standard of practice or usual

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

care, or you could have three or four alternative methodologies implemented in different, similar contexts, and then you'd be monitoring them to see which is the most effective, both at the overall population or overall level, but also you can do subgroup analyses.

It can be generating new data or it could be going back to prior data in a retrospective sense. But I think what we'll be talking about is prospective studies, and in contrast to kind of the classic gold standard of randomized, controlled clinical trials, this is an approach that uses a much broader population implementation strategy to determine which methodology is most efficacious at the population level.

So in this example here, the IOM, in looking at a variety of research priorities which they set, 100 research priorities, they felt that about half of them would be best addressed through comparative effectiveness

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

research, whereas the other half, randomized trials might be more appropriate.

In this paradox, the clinical trial is the best way to sort of formally determine if some interventions work, but it doesn't necessarily tell you that the population will benefit from those interventions. You'll notice here actually these slides pulled off the web, if you just put in "comparative effectiveness research" and .pdf to get slides. You get all these great slides.

These slides happen to be from RTI.

RTI, of note, is the coordinating center for the REDS III program, and so you'll hear a little bit about that at the end, about the possibility that through RED III, there may be an opportunity to use the REDS III network and coordinating center to help monitor nationally initiated efficacy trials, or effectiveness trials.

So again, in terms of juxtaposing sort of randomized trial efficacy studies

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

versus the concept of effectiveness studies, efficacy studies are large, expensive focused protocols, which drive return visits at regular intervals, blinded studies, whereas effectiveness studies are really just monitoring practice and reality in the field, and typically there is no blinding, no modification of treatment.

The patient populations in efficacy trials are often quite restricted, and the criteria for enrollment are highly selected, in order to be sure you're looking at homogeneous populations, selected populations, no comorbidities.

Whereas these effectiveness trials are really representative of the real world. Study sites, often efficacy studies are done at a restricted number of academic centers, whereas effectiveness studies are done in the broad clinical setting, in our case, the national blood collection facilities.

Sample sizes are typically

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

relatively small and they're powered to a discrete outcome, whereas the sample sizes for effectiveness studies can be massive, and really enable large subgroup analyses.

In end points again, efficacy studies tend to have discrete, primary end points, some secondary end points, whereas in effectiveness studies, you're really looking at routinely captured data or, in some cases, a small additional data elements that might be captured to inform relevant clinical decisions.

Just a final side. The duration of efficacy studies are often short, because these are expensive interventional studies, whereas effectiveness studies can take place over one or several years, in order to really evaluate the impact of several different alternative strategies with respect to the effectiveness, not only in reducing an adverse event, but also compliance and impact and, in our case, on the blood supply.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Again, an efficacy study is usually a randomized trial type design, whereas effectiveness studies are usual care versus some alternatives. Data collection, in the case of sort of randomized trials or even observational studies using specific instruments, and often selected additional test parameters, whereas effectiveness studies are essentially capturing routine data, generated off of routine donation visits.

The analysis can be variable, depending on the design. But most important is, you know, an efficacy study will give you information specific to the population that was recruited into that study, whereas these effectiveness study designs are really intended to give broad, generalizable information. So with that, I'll pass it on to Brian.

DR. CUSTER: Thank you. So first of all, I'd like to thank Dr. Davey and the organizers for allowing us to present. The

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

next thing that I'm going to present, my part of this presentation, is to just sort of show you the kind of data that we capture at Blood Systems, and how we can analyze that.

Important, I guess, to sort of set the stage for that is beginning in September 2009, we initiated HemoCue 301 use on all of our donations at the time of presentation. So we have quantitative hemoglobin values available. Obviously, they're finger stick hemoglobin values. But we have them available for that time period.

That includes the people who are also deferred. So we're able to, I think, provide some additional insights into some of these topics than what's already been presented. Also to set the stage, in addition to talk about whole blood, I'm going to talk about double red cell collections and also multi-component procedures. So this is a breakdown for this entire time period of the various donations at our organization. The

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

vast majority, of course, are whole blood collections at 76 percent, but we have a substantial number of double red cell collections comprising 14 percent of our collections, and a fairly significant number of multi-component procedures.

This also helps, I think, to understand a little bit. Because we have the use of the apheresis technologies, our distribution of who donates what is perhaps different than at other centers. In particular, for whole blood, 60 percent of our whole blood collections come from females; only 40 percent come from men.

You'll see that for multi-component procedures. A majority of the collections are for males, and that's even higher for double red cell collections, with almost 85 percent of the collections for males. But overall, it's still approximately even between the genders, in terms of people we collect from.

Then just to sort of summarize one

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

specific year, and I am mixing between sort of that entire time period of September 2009 through July 2011, and also data for just 2010, just because of the data sets that were sort of available. But to sort of say during this time period, there were 685,000 presentations made by 428,000 donors, with 1.6 presentations per donor.

Specific to red cells, there were 558,000 red cell collections from 342,000 donors. This represents 70 percent of all of the red cells produced by the organization, and an average donation rate of 1.63 donations per donor per year.

Important: These are two, I think, important sets of data to sort of keep in mind. 16 percent of our donors made more than two donations in 2010, and 7.5 percent of our donors made more than three donations, and accounted for 20 percent of whole blood red cell collections. During that same time period, over 52,000 donors were deferred for

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

low hemoglobin level, overall deferral rate of 7.6.

That would be totally expected. The vast majority were females who were deferred, about 12 percent, but 1.3 percent of presenting donors who were male were also deferred for low hemoglobin.

Looking now just at actually our first-time donors, just to give sort of an indication of our sort of population, you can see that the mean hemoglobin in first-time donors in men was 15.9, with two standard deviations represented there, going from 13.3 up to 18.4.

As you would expect, it was lower for females. It was at 13.8. I should make clear that this is -- this does include people who were deferred, so these are really sort of the entire picture in the population.

Breaking that out actually by age group and gender, you can see that for males, as has sort of previously been presented by

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Dr. Mast, that as you age, that mean hemoglobin level in first-time donors at an older age is going down a little bit, and goes down a little bit more.

Similarly, with post-menopausal women, it does go up, but it doesn't go up anywhere near to obviously what males have as their average set point. I think the important thing is just to say that really, trends across the ages are fairly similar.

This is a sort of reiteration of also similar information that's been shown. But I think it's also a little more instructive. So if you keep in mind that the average for men is 1.3 percent of presenting donors who are deferred, and for females it was 11.8 percent, you can see that that's in excess. At younger ages, child-bearing age for women. Then it decreases.

But the key is that our deferral rates in men never approach those of what we actually see in women across any age group.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Looking at this by also race ethnicity, clearly also well-known facts already, but just to present them, to put this in perspective, that black males and black females have a lower average set point than other groups, other race ethnicity groups, and the one thing I think is a little bit interesting is that I'm not showing that the standard deviations or confidence intervals around this.

But for white females, compared to other females, other than blacks, they're a little bit higher and a little bit lower for Hispanic or mixed or Asian and Pacific Islanders. On the opposite site is that for males who are white, there are little -- I'm sorry. The females are a little bit higher. For males, they're a little bit lower than the other groups that I just mentioned.

7.9 percent of males who were black, non-Hispanic had a hemoglobin between 12.5 and 13.4, and 8.8 percent of females had

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

a hemoglobin between 12 and 12.4.

All right, so of course that translates into differences in deferral rates by race ethnicity groups, and that is definitely shown here, where these, on the top panel, is whole blood presentations.

On the bottom panel is double red cell collections. The all is the same color as our new color template, so it's a little bit lost. But the green bars represent all. So as you would expect, the highest rates of deferral are in the black population, and particularly for black females. But also, there's an excess for black males also.

You can see the distributions. Always obviously there's an excess for females relative to males in terms of deferral, whether it's a whole blood or double red cell collection. We see this pattern, and I know that other people have talked about it. So this is now just trying to orient you a little bit.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Looking at people only within the year of 2010, but people who had at least six presentations or presented six times, what the hemoglobin, mean hemoglobin value was at the first presentation, second presentation, so on and so forth. What this shows is that the slight decline that you'll see, and I'm going to show some more data on that in a minute.

But after you get to around the third presentation or third donation, then you sort of -- I think you select it for those people who can sustain that level of donation, or some other things are going on.

But this is actually true, whether it's males or females, that you don't see a decrease thereafter in hemoglobin values in the population. The relative numbers, of course, are small in terms of the number of people who are providing six donations a year.

This is actually a busy slide, and so I'm only going to point out a couple of aspects of it that I think are important.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

One is, as you might expect, particularly this hemoglobin level being less than 12.5, so people being deferred with four donations. It's about 13 percent of the population who presents are deferred. With five, it is 16 percent. With six, it is 19 percent. So yes, there still is clear additional deferrals going on with higher level intensity of donation.

That, I just pointed out, was actually for females. For males, it's 2, 2, and 3, so not necessarily a specific trend being evident for males. Interestingly, I think that there is clearly, you know, selection about who can tolerate a frequent donation, and then there's also selection about the blood type.

In this particular case for females in particular, 52 percent of females were Type O who gave four times a year. By the time you get to six, it's actually 57 percent of females. So there would potentially be

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

some impacts and changes in donation intervals on O availability, at least in our system.

This is a summary table, and I'm just going to quickly go by. I just wanted to be able to provide the numbers in case you wanted to see the actual numbers I've shown here in the same way. So once again, to sort of set the stage for what this is, at the top are males. All males are in blue. That's sort of obscured by the green line, which is all males who gave by whole blood donation, and then double red cells. These are the mean hemoglobin levels.

You can see, what we see basically is that each successive donation, there's about a .1 to .2 grams per deciliter decrease in the hemoglobin level, and I should say that this begins with an artifact, and the artifact is that we required, on your first donation, that it have to be successful.

So you actually have to have had removed some degree of, some amount of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

hemoglobin and associated iron. So the first drop may be a slight artifact, but nonetheless I'm pointing it out.

It's important for the next sets of slides I'm going to be showing, because the way that we analyze this data was to say with the presence of donation, what then happens? What are the risk factors for subsequent deferral?

But as you would expect, so females are always lower than males, but generally in parallel. So we just see this sort of downward trend over time, with a total of ten presentations represented. This is across the entire time period that we have the data set available.

I should make that point and I didn't make it before. All hemochromatosis donors were actually excluded from all of the analyses we're presenting here. So they are not driving any of the results.

So this has been discussed and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

obviously RISE and the REDS group have presented on this already. But looking at our own system, about this combination of where do you start with your hemoglobin, and what is the impact of when you return to donate, on the likelihood of being deferred.

So these are the index hemoglobin values shown right here. This is not supposed to be seven; it's just supposed to be greater than or equal to 15 grams per deciliter.

But if you're in that category, whenever you come back, even if it's as soon as eight weeks, there's a very low probability that you're going to be deferred, and actually I would say it's pretty similar all the way up to, or all the way down to 14 grams per deciliter. These are really quite similar.

The transition seems to be this blue right here. Between 13.5 and 13.9 is where you get that clear duration is important, and that coming back a little bit later than eight weeks and particularly after

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

12 weeks, you see a lower likelihood of deferral. There still are deferrals.

For people who sort of started with a relatively set point anyway, their probability of deferral is quite high, no matter when they come back, and I'm going to show some slides on that that I think exhibit that even in more detail.

The rates of deferral, based on duration of coming back, were 28 percent, 16 percent, and then decreasing all the way down to zero percent in the group that's good on 15. So this particular analysis is only looking at two donations: the index donation that had to be successful, and then what happens next.

So it had to be successful, but then again this is time plot. So we're looking at paired donations over time, so with that initial successful donation, then people start coming back. If they had a very low hemoglobin, these are these people who are

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

already deferred, and they come back. They are deferred again at a higher rate. You would expect that.

The key point is that for the people who actually were accepted for donation, anybody above 12.5, that the duration is a little less important, at least in what we're seeing. So that if somebody comes back at 20 weeks, there's sort of a linear relationship, even at 80 weeks.

So that the person who came back at 20 weeks has the same probability of being deferred as the person who comes back at 80 weeks, if they are in the same baseline hemoglobin or index hemoglobin category.

So we looked at this actually in the same for double red cell collections, a similar sort of situation. Obviously these people who are low to start, that's a unique set of people, and what has happened is that they were successful. Then they come back, and then it's their next donation after that,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

so they were successful.

Then they were deferred, and then, based on that previous hemoglobin value, it's highly likely that they're going to be deferred again that third time that they come back.

But for the people who actually were eligible to donate, you see this sort of similar relationships always, and I know that the color coding is a little bit hard to follow. But always, of course, at a given hemoglobin group, the likelihood of deferral is much higher for women than men.

This is the same for the multi-component. It's a little more complex, but the patterns are generally the same. So what I want to do is actually spend the last bit of my time talking about this analysis that we did, this regression analysis.

So what we did was a random effects logistic regression analysis for longitudinal data. So what that actually is is we're

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

trying to account for there's clearly correlation within subject.

So we're coming for the panel data that we have, but that is also correlation within subject. Meaning somebody's hemoglobin value is their hemoglobin value. There's probably some set point that you're working against anyway.

So we did an analysis where, a multi-variable analysis where we looked at a successful collection at index in the data set, and then followed them and said what are, what is the likelihood of deferral, or what factors, risk factors are associated with being deferred at your next presentation, across the entire time period?

So this is looking across time. We did separate models for whole blood, double red cells and also for multi-component. All of those models came in the same parameters, which are hemoglobin at last presentation in categories, which I'll show you in just a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

second, the elapsed time or interdonation interval, also in categories, the donation site.

That's fixed, mobile bus or mobile set up, age group, sex, race, ethnicity and also blood center, and it is actually true, as other people have commented on. There's always a center effect, and it's really hard to work through.

So that I'm not trying to hide that we have a center effect. We do see differences in the likelihood of deferrals and the odds of deferrals at our centers, based on the location. But I'm not going to show that data. It's not as dramatic as has been seen for the REDS II data.

All right. So it's busy. What we have is one model for double red cells at index, multi-component at index, and also whole blood at index. The key thing about this is that so this once again is looking across all donations. So once again, as time

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

goes on, you could have started. You were successful as required for entry into our database, but then the next time you come back, you were deferred.

So that's why you can actually have an odds ratio of another deferral. So if you have something that is hemoglobin level that causes you to be deferred, your odds, regardless of the collection type, of being deferred are very, very large, 27, between 23 and 27, essentially the same, regardless of the collection type.

For those people, though who are sort of around the borderline of what might be considered an acceptable hemoglobin, still your odds about next presentation, after statistically controlling for everything else, are much higher than at that next presentation. You will be deferred. These are much more impressive odds ratios than the duration effect, and I'm getting to the duration effect right here.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Certainly not to say that the duration effect is not there. It clearly is.

It's definitely a statistical relationship, in that the sooner you come back, the higher the odds of being deferred for the multi-component, and for whole blood, the numbers are really very similar.

You can see that relative to coming back after a 24-week time period, if you come back within 8 to 12, you have about a 2.8 or approximately 3 odds higher risk of being deferred.

You can see that the numbers that are represented each of these models. So those are sort of the factors related to actually what blood centers are doing, and they're sort of the factors are inherent in the population itself, sort of where they're presenting to donate. There really isn't anything statistically important going on there.

Slightly lower risk of being

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

deferred at mobile set-ups and mobile buses. You would expect that in that, actually the fixed clinic. There's easier opportunities to go back and mobiles go at specific time intervals.

Age effect. We only see an age effect related to the odds of being deferred in the whole blood population, which of course is the largest one. There is clearly still a gender effect, and it is in the range of three to four times higher risk of being deferred.

The key thing here, and I think that what sort of is important, is that by including the previous hemoglobin value in these analyses, we do not see an odds ratio of ten for gender. We see an odds ratio more in the range of three to four. So I think that there's some uncontrolled confounding that we always have to think through, and these are difficult to do. But our data sets that are available allow us to do that.

We of course see that relationship

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

that you would expect with ethnicity and in particular blacks being far more likely to be deferred at the next presentation than whites, in comparison to whites.

So these models, I guess, what they help us do is at least understand, within the data sets that we have available and the kind of information that we capture at Blood Systems, how we can sort of analyze that.

What it, I think, does speak to is if we were to try to assess potential interventions to reduce the threat of hemoglobin, recognizing that this is a threat of hemoglobin deferral, recognizing that this is a different question than iron sufficiency, the kind of data that we have available, that would permit us to assess potential interventions.

With that, actually I will turn to Dr. Kamel, who will actually present on those thoughts that we've had in our organization.

DR. KAMEL: So here, I will try to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

present to you approaches to study in the comparativeness effectiveness, as Mike has alluded to. Before we start, I thought it may be helpful to just review a few of the facts that we've heard and learned over the past couple of days.

We know that there is hemoglobin set points and this could vary by gender, race, ethnicity and other personal determinants. Over the past two days, we learned that anemia is a late manifestation of iron deficiency. Iron deficiency, we see it in donors, even first timers who have acceptable hemoglobin levels.

Blood donation contributes to iron deficiency in some donors, and educating donors is difficult and behavior modification to increase iron stores may be even more difficult. We believe that donors will make one or two donations a year, maybe able to sustain their iron balance through enhanced absorption of dietary iron.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Again, Brian mentioned it, but it's worth emphasis, that only 16 percent of donors made more than two donations in our system in 2010. Eight percent of donors made more than three donations, but they accounted for 20 percent of whole blood red cells.

In the multi-variable model, Brian showed the likelihood of deferral at the subsequent presentation is lower, with higher hemoglobin level at previous donation, and is lower with longer interdonation interval. But the interesting point, the hemoglobin at previous donation was more strongly associated with deferrals than the interdonation period.

Among donors with hemoglobin of 12.5 to 13.4, it was knowing that again 52 percent of men and 57 percent of women were iron deplete and this data was shared by RISE group and Dr. Barbara Bryant has similar data as well.

So what can we do to mitigate iron deficiency in blood donors? Again, nothing

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

new here. All these possible interventions have been discussed earlier back and repeated over the past couple of days.

Donor education, dietary recommendations, modification of hemoglobin acceptance criteria, modification of interdonation intervals, and measuring ferritin in donors and iron replacement.

One or more of these medication strategies could be applied to either all donor universal, but is that necessary, or should we target interventions to group at risk? Women at child-bearing age, donors with lower acceptable level of hemoglobin, 12.5 to 13.5, or donors with iron deficiency and low ferritin.

In implementing any of these interventions, obviously we should be cognizant of operational issues and logistics, computer system support and definitely blood availability. The first approach is to modify the number of donations per year. Here, we

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

are maintaining the current hemoglobin acceptance at 12.5 for both male and female, but we limit donations for men at four and for women at three by adjusting the interdonation intervals to 12 or 16 weeks.

This approach, which I call it M4 F3, will result in our system in a five percent presentation losses. Obviously, that relatively speaking, would be a modest loss, compared to any other more restrictive donation frequencies. But again, it will prevent capable donors as we've seen, who have donated four, five and six times, will prevent them from donating blood.

In such a case again, we think that a comprehensive nutrition education for all donors will be necessary. Again, one reservation about that model, that model existed in different European countries. Some of them even have higher hemoglobin acceptance criteria. Some of them collect less than the 500 mL of whole blood, and in these country,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

still iron deficiency in blood donors remains.

The second approach is to use pre-donation hemoglobin to define interdonation intervals. If it's gender-neutral, we will keep the minimum hemoglobin acceptance criteria at 12.5 for both male and female, but the interdonation interval increases as the donation hemoglobin decreases.

Just for reference, these are numbers in our system in 2010, so one can very much estimate the effect. So here, if we are to apply extended integration intervals for donors in this group, there will be like six percent of our male donors and almost 30 percent of female donors will be affected by such an extended interdonation interval. Donors with 13.5 and above can donate at eight weeks interval as of today.

The third approach introduces ferritin testing to a group of donors. So we'll do a ferritin testing for a donor with low hemoglobin, to define interdonation

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

intervals. We will maintain the current hemoglobin acceptance at 12.5, and the minimum interdonation intervals at eight weeks.

We'll identify donors at greatest risk for iron deficiency based on hemoglobin.

We will measure ferritin in male and female donors who successfully make a red cell donation, and whose pre-donation hemoglobin falls between 12.5 and 13.4.

In those identified with low ferritin, we will reduce the allowed annual donation by extending the interdonation intervals for that group. Again, based on our 2010 data, we will perform about 146,000 ferritin tests, and just considering that 45 percent of those will be identified with low ferritin, then there will be about 64,000 donors will be affected by lengthening their interdonation interval.

One can refine this approach by applying or running ferritin testing only on frequent donors.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So here again, the hemoglobin acceptance limit at 12.5, interdonation intervals remain eight weeks. But we will identify donors at risk of iron deficiency in frequent donors. So a donor who donates two or three times in 12 months' period, we will do ferritin testing, and again those who are identified with low ferritin, we will apply extended interdonation intervals for them.

The advantage of testing only frequent donors who donated more than two times, it obviously will reduce the number of ferritin testing, essentially again in our system will cut testing by 60 percent.

And again, obviously people who donate one or two times in a year are generally at low risk of iron deficiency, at least if they are iron deficient. We don't think it reduces their blood donations.

In both Approach 3A and 3B, we define if ferritin is less than 13 in males or less than 20 in females, we will apply

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

extended interdonation intervals. We are considering 16 weeks. We will counsel donors that your iron stores may be marginal. If you want to donate more frequently, you may consider over-the-counter iron preparations.

We conclude by just a few remarks here. We are proposing to do a CER, to assess the impact of several possible changes to red cell donor qualifications criteria that are intended to reduce donor iron loss and hemoglobin deferrals.

Our data supports use of pre-donation hemoglobin levels and possible prior donation frequencies to target interventions to donors at greatest risk of deferral and iron depletion.

A comparative effectiveness research protocol of proposed or other intervention would be conducted for two years, to evaluate the impact on donor deferral, iron status and blood availability.

As Mike mentioned earlier, REDS III

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

could potentially assist in design conduct and data analysis. That's all what I have, and we will take any questions.

(Applause.)

DR. KAMEL: Related to random effect regression analysis, Brian is still in the room.

DR. GLYNN: Steve, you have a question?

DR. KLEINMAN: Yes, a question I think for you Hany. Just the idea of comparing different approaches, I'm really unclear what the outcome variable would be. I think it was in your last bullet, that you could assess the degree of iron deficiency in your donors, degree of hemoglobin deferrals. Those might be reasonable.

I don't see how you could assess blood availability, because any blood center that adopts a strategy that loses them units, they're going to find a way to replace those units. So I think that would be a really

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

confounded variable but, you know, obviously we could think about it more.

But what was your initial thinking about what you would actually be able to compare between different approaches, that would be valid outcome variables?

DR. KAMEL: Yes. Obviously, the three approaches, as presented, they are presented at very high level, and need more refining. For instance, we mentioned what level of ferritin. We heard from Joe Kiss that one level of ferritin is adequate and so forth.

The main outcome that we'd be looking for, again as part of the CER, is the simpler outcome, the better to monitor. So maybe that's hemoglobin deferral, before and after, or if more than one organizations are implementing different, one of these approaches, we can compare between Organization A, Organization B.

But hemoglobin deferral, we can

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

look at the variables, if there are any changes and so forth.

DR. BUSCH: Richard raised the concerns that we would dip into younger donors and more first-time donors and ID marker rates. So I think all of those could be donation population.

DR. KLEINMAN: The demographics of your population, the demographics of your accepted donors.

DR. BUSCH: Yes, of the donors.

DR. KLEINMAN: And also collections outcomes. You could also use it to see within the operational constraints of a particular blood center, you can accommodate any changes in the reduction of blood availability. You said that we couldn't use that as an outcome variable, but I actually think you could if you're looking at the net effect.

If we know we're going to lose five within the constraints of normal recruitment and things like that, can we get back to the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

baseline?

DR. GLYNN: Thank you, Dr. Kamel. All right. Our next speaker is Dr. Forshee. I'm sorry. So Rich is the Associate Director for Research for the Office of Biostatistics and Epidemiology in the Centers for Biologics, Evaluation and Research at the U.S. FDA.

He works on a wide range of issues related to the risks and benefits of blood and blood products, and Rich's talk today or this afternoon, or his title "Impacts of Any Changes in Interdonation Interval on Blood Availability."

DR. FORSHEE: Thanks so much, Simone. Good afternoon everyone. I really appreciate the opportunity to speak with you again today. What I'm going to be discussing this afternoon is some modeling approaches that we've been developing, in order to -- thank you.

Some modeling that we've been developing to try and estimate potential

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

changes in blood availability, the number of blood donations that we would see, if there were any adjustments in either the interdonation interval or the hemoglobin cutoff requirements.

We thought that it was important to model both of these in the same system, because if we make any changes to extend the minimum time between donations, that's going to affect the average hemoglobin level that people have when they return to visit, and may affect the number of deferrals for low hemoglobin that we see. So we've tried to build an integrated model.

Before I start getting into the details of the modeling, I want to thank all the many people who have contributed to this effort. I've been working very closely with the REDS-RISE analysis working group for the last, I guess it's been almost a year now that we've been working together, and in particular Bryan Spencer and David Wright have been very

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

generous with their time, and with helping to develop some of the data and models that were necessary to populate the parameters of the model that I'm going to be discussing.

Anne Fernando, who's on the faculty at Norfolk State University, joined us for the summer, to help work on this model, and my colleagues at FDA, including Arianna Simonetti, who's with us today, Mark Walderhaug and the rest of the team in my office have been great to work with.

All of us in this room know the background for today's conversation. There have been a number of discussions about whether to make changes to either the minimum interdonation interval, or the minimum hemoglobin finger stick test requirements.

We've heard some other suggestions over the course of the last two days. We know the changes in these may affect the number of units that are collected, and we want to have some flexible way of estimating what this

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

impact is going to be. And as I mentioned, there's an interaction between the minimum time between donations and deferral for hemoglobin.

So what I'm going to be doing today is providing the first public look at a compartment modeling approach that we've been developing, in order to estimate the potential blood donation loss. What I'm hoping is that this will help us to start a discussion about how we can use this model, so that all the stakeholders can discuss what the impact of any of these changes would be.

The results are preliminary, because we still need to understand exactly what questions we want to address with the model, and currently the model is only going to be looking at returning donors. So if we wanted to -- we think that's going to be the group that's most affected, but if we want to expand the model later, that would have to be an extension of what we've currently done.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

For those of you who aren't familiar with compartment models, compartment models are a way of addressing the dynamics by which people move in the population. So with a compartment model, you divide a population into different subpopulations, and then you model the rates at which individuals move from one of the subpopulations into another.

Compartment models have been widely used in a number of areas. They really got their start in modeling infectious diseases, but they've been used in a number of other places since then. Mathematically, we wind up using differential equations in order to predict how many people will be in each of the compartments at any given time period.

For our purposes, we've developed a compartment model of returning blood donors with compartments for eligible donors, the donors who have been deferred because of a low finger stick hemoglobin test, and the donors who have been deferred after a successful

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

donation.

So this is a view of what a compartment model will look like, and here I'm showing a simplified view, so that you get an idea of how this system works. Here, we're only showing two compartments. We're showing the deferred donors who have successfully donated and are waiting to become eligible, and the donors who are eligible to donate, they could show up any time, and the actual time that they donate will be based on the behavioral data that we have.

So we'll have a number of people in each one of these departments, each one of these compartments, and then we're going to calculate the rate of flow between them. I'll start with the rate of flow from the deferred donors who are waiting to become eligible.

There's a mandatory requirement currently of 56 days that people must wait after they donate. We want to get the average daily rate of flow from this department back

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

into the eligible. So this can be calculated simply by taking one divided by 56 days, to get the percentage of that compartment each day that will become eligible to donate.

I should emphasize this is the average rate of flow between the compartments, and that's what we're going to be focusing on.

For the donors who are eligible to donate, it becomes a little more complicated, because we have to calculate a weighted average of how long people are going to wait to donate after they become eligible. I'll show more about that later, but we base this on actual data from REDS II, about the number of donors who show up at each one of the possible days that they could donate.

Finally, we're going to be counting the number of times that people move into this deferred first successful donation, and this count is going to tell us how many blood donations have actually occurred.

So I've already tried to give you

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

some understanding of why we have 1 over 56 as the rate of flow, out of the deferred first successful donation. What we're trying to do here is come up with the average daily rate at which people move out of the compartments. So since we have, since we're looking at the average daily rate and we know everyone is in that compartment for 56 days, on any given day 1/56th of the people in that compartment will move out and become eligible to donate again.

Then we use a similar logic for the rates of flow out of all of the other compartments. So what I showed was a simplified two compartment version of the model. But we also need to take into account hemoglobin deferrals as well.

In particular, we need to have a way that we can estimate how lengthening the minimum interdonation interval is going to affect the probability that someone will be below, will be deferred for low hemoglobin. As we make people, as we make frequent donors

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

wait longer between donations, some of those donors who would have been deferred if they showed up, for example, 56 days after donation, if they have to wait an extra 14 days. Some of those people who might have been deferred for low hemoglobin will have recovered enough that they could successfully donate, and we want to take that into account.

The way that we did that was by working with the REDS-RISE analysis working group, to develop a model of hemoglobin levels. The REDS data contains -- the REDS data set contains data on the hemoglobin level, and the time since last donation.

We were able to develop a regression model as a function of time since last red cell donation and a couple of other control variables that we included. I talked about this in detail yesterday morning.

So now based on this information about the probability of being deferred for any given length of time since the last red

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

cell donation, we can divide up the number of people presenting to donate, which we calculate based on the distribution of donors and time since last donation. So that a certain percentage of them, defined by our model of hemoglobin levels, will move into a deferred for low hemoglobin.

The rest will move into a successful donation and deferred for a minimum time period, and the people who are deferred for low hemoglobin, we also have data on how long people wait before presenting again, and from that, we're able to calculate a weighted average of the time that it takes before they are able to successfully donate again.

So we now have our complete three compartment model that shows how people move among these different states. I briefly want to mention how we calculate the weighted averages, and here I'm going to be focusing on the weighted average from the eligible to donate to presenting.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

The basic idea is simple. If we want to know the average time that someone spends before they donate, we want to multiply the number of people who wait 56 days times 56, plus the number of people who wait 57 days times 57. Add that up across the whole group, and divide by the total number of people who are presenting to donate.

So this is easy to do when we're at day -- when we are the status quo. It becomes a little more complicated when we want to estimate how long this period is going to be, if we increase the minimum time between donations.

We know that people are then going to have to wait longer, and we use the simplifying assumption here, that anyone who was donating at less than the new minimum that is set, will now donate at the new minimum. So in terms of the notation that I have here, if someone is donating at less than 56 plus t^* , however many additional days we add, all

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

of those people are now going to donate at 56 plus t^* .

To actually calculate this, we can simply split the numerator into two pieces. Anybody who is currently waiting 56 plus t^* days, so whether that is 56 plus two weeks or 56 plus four weeks, we're assuming they aren't going to be affected. They're still going to come, they're still going to show up and donate at the same interval that they had previously.

Everyone else, however, who was donating at less than 56 plus t^* days is now going to be forced to wait until that new minimum interval between donations. So we can just multiply everybody who was less than equal to the new minimum times the new minimum, to get that portion of the numerator, and we can get our new estimate of the average time between donations.

For those of you who just want to know what the answer is, this is the graphic

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

that tells you how that time between donations will change. So at each period, we force more and more people to wait a longer period of time, and we get this nice, smooth curve up as we increase the additional days of deferral.

As I mentioned, we also need to take into account the people who will no longer be deferred, because they've waited longer and their hemoglobin has had a longer period to recover. As I showed yesterday using the model for hemoglobin that we have developed, we can calculate curves based on any cutoff that we would want to examine, that shows the probability at each day that someone will be deferred.

We can then use this probability for each day since last donation that someone would be deferred, multiply it by the number of people who show up on that day, and get an overall probability of deferral at any new minimum time between donations.

This shows that calculation, and we

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

show that at the current 12.5 cutoff, and here we're looking at males. We can see that there is a slight decrease over time, but it's not terribly pronounced in terms of how much the overall probability is reduced. If we were at a higher percent cutoff, we get more people who we recover, who are no longer deferred because of a low hemoglobin value.

The last piece of this is to calculate how long people are spending in the low hemoglobin compartment. It's important. We're going to take a weighted average here again. However, we don't have to worry about shifting any people. We're assuming that people are going to have the same behavior in the deferred for low hemoglobin as they currently have.

I'll just mention that I've left out some of the math. Some of you will be disappointed by that, some of you will be grateful. If you're disappointed, we can talk about the details later.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So this is a chart that looks at the distribution of the time that people wait after hemoglobin deferral. Here, we're looking at the distribution for males. You can see that we have a lot of people who show up within a relatively short period of time after they've been deferred, but the tail goes out to a very long distance.

The average time for males, before they present again, is 63.8 days. The overall pattern is similar for females. There, the average though is 79.3 days. This gives us all the pieces that we need to estimate the compartment model that I described earlier, and these are the results that we get for males, in terms of the predicted reduction in donations compared to the baseline. Here we're using the 12.5 cutoff just for an initial average.

We can calculate this for any given number of days that we would want to see. Here, I pulled out two particular values. At

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

14 days, this model is predicting that we would lose about 1.3 percent of returning male donors. If we extended an additional 28 days, the model is predicting a reduction of 3.7 percent of returning male donors.

We have also calculated this for females at the current 12.5 cutoff. There, the reduction in the percentage of returning female donors is less. We see a 0.6 percent predicted reduction at 14 days, 2.0 reduction at 28 days.

I want to emphasize that here I'm showing only two of the possible groups that we might want to look at. I limited this because of time limitations. But we've actually built a model in such a way that we can look at very specific strata that we might be concerned about.

So we have the model built so we can look at the effect on African-American donors. We have the model built so we can pull out specific blood types, such as looking

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

at O negative or the entire O blood group. So that the model is built in a flexible way, so we can split it out in terms of men and women, African-Americans versus other races, any of the individual blood types that we might want to compare, as well as looking at any hemoglobin threshold that we might be able to -- that we might care to look at.

So we think this model is presenting a very flexible way that looks at some of the important interactions between minimum time between donations and hemoglobin levels. We think that this is going to help us to explore what the blood donation loss might be for any changes that we might consider in these two factors.

As I said a second ago, the future work is going to include stratification by blood type and race, ethnicity, so that we can consider some of the important subpopulations that we might -- that might be of particular concern. Currently, we began the model

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

looking at returning blood donors, because we thought those were going to be the group that was most affected by the changes that we were discussing, but the compartment model can be expanded to include capturing first-time blood donors who might be recruited, as well as blood donors who leave the system because they stop coming back for blood donations.

With that, I'll just thank you for your attention, and we probably could answer some questions now or the questions could wait until the panel discussion later. Thank you.

(Applause.)

DR. GLYNN: I guess no questions, so thank you very much. Our next speaker is Dr. Sayers, who is the president and chief executive officer at Carter BloodCare. Merlyn serves on the faculty in the Department of Pathology at the University of Texas, Southwestern Medical Center in Dallas, and Merlyn will talk to us about predicting the effect that lengthening the red blood cell

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

interdonation interval would have on your community blood centers.

DR. SAYERS: Many thanks Simone, and also thanks to Dr. Illoh and Dr. Davey for allowing me to barge in on this presentation.

I say "barge in" because this is the point where we descend from the lofty intellectual heights that are occupied by Drs. Busch and Kamel and Custer and Forshee, and we take a view of what is going on from the trenches at the community blood program, where what we're interested in is safely maintaining the availability of the blood supply.

So as Simone said, I'm going to be looking at how we might predict the effect that lengthening that interdonation interval is going to have on how we manage inventory. So no, I'll use this. I'll use this. This is fine.

I actually have to confess here that this is an illustration that I used in a presentation a couple of weeks back, and it

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

was headed "Anticipating the Perfect Storm." This was a presentation to hospital administrator and hospital physicians, and the perfect storm that I was trying to describe to this group had to do with what looks like a confluence of events over the next few years, which is going to significantly influence the confidence with which we can predict the blood supply will continue to be available.

I'd be the first one to grant that calling this "Anticipating the Perfect Storm" is at best melodramatic and at worse hysterical. But I really wanted to get this group's attention, because I do believe that there's this narrowing window of opportunity, where we need to come to grips with what we consider the availability of the blood supply.

What are those elements, then, that are contributing to what I see as challenges to availability? Well, the first is should the shelf life be shortened, and when I made this presentation, I referred the group to an

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

editorial by Simone and another by Paul Ness, and an article by ourselves, which is available as an early view online presentation in Transfusion, having to do with should the shelf life be shortened.

Because when you look at those randomized prospective control trials that are being conducted at the moment, the \$80 million worth of investment in research, I would be very, very surprised if those trials do not reveal that there are indeed some categories of individuals for whom fresher blood is indicated.

I'd be very surprised, and I think if some of those categories are identified, I think the prediction of Sunny Dzik and others, that if it's good enough for some categories of patients, that they deserve fresher blood, then surely fresher blood is deserved across the entire spectrum of the transfusion dependent population.

If those predictions do come true,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

then the shortening of the shelf life will dramatically influence our ability to maintain an adequate blood supply. Then I also referred the group that I was talking to to the presentations here today, this workshop, and the recent Blood Products Advisory Committee meeting back in July addressing, as we know, hematocrit and hemoglobin acceptance standards, and the issues having to do with the interdonation interval.

So let me tell you what the setting is, where we watched what was going on and tried to make predictions from the trenches. So the setting is Carter BloodCare. Our service area is Dallas-Fort Worth and the surrounding 57 counties. Now I have to concede that much of the conduct in Texas is idiosyncratic, but I would like to comment that when I compare our experience in Dallas-Fort Worth with experience in other large community blood programs, I don't think there really is a center issue when it comes to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

looking at what the effects of the interdonation interval might be. We serve a population of about eight and a half million.

Our collections are about 400,000. Something I would comment on though, that was hinted at by Richard Benjamin yesterday, and that has to do with how blood programs are looking at changes in the blood supply.

In Texas, and I think Susan Rossman would probably vouch for this as well, we have not seen the downturn in the economy affecting hospital demand for blood and components. In fact, what we've seen in Texas is not so much a constraint in needs, but what is tantamount to increasing hospital needs, which has made concern for what might be issues affecting availability, has made our concern even more heightened.

So these are the questions then that we asked when we took this view of what an interdonation interval lengthening might have as a message for us. We asked what

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

percentage of red blood cells would be lost by ABO and Rh, at three different interdonation intervals. I cannot exaggerate how important it is, when one's looking at past experience or predicting future experience or drawing up models, how imperative it is, I can't exaggerate this, how imperative it is to make sure that ABO and Rh considerations are taken into account.

Then the second part of that question was had to do with we chose the lengthening of the interval to 70 days to 84 days or to 112 days. Some of those intervals were referred to in that Blood Product Advisory Committee meeting that I spoke to you about earlier, and also we chose 84 and 112, because those are time periods, the interdonation intervals in other countries.

So think of it this way. If that interdonation interval was lengthened to 70 days, that means the maximum number of times an individual could donate a year would be

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

five. So we would have to exclude one donation from the individual who donated six times a year, and at 84, there is the interdonation interval means that we would have at maximum four donations a year.

So those individuals who were donating five times a year, we'd lose one donation from them, and those individuals that had been donating six times a year, we'd lose two donations from them. Then at 112 days, we would exclude one, two and three donations from those super-donors, who were donating four, five and six times a year.

We did, in the analysis, make some assumptions. One was that we would not be able to increase the frequency of donation of the donors that were left, those one, two and three times a year donations, donors, if the interdonation interval was lengthened, and that may or may not be true.

What I can say is that we bend over backwards to try and ensure, within the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

specific blood types, that individuals donate as frequently as possible.

We also assumed that if there was a change in the interdonation interval, that those individuals who might now be discouraged or prohibited from donating and extra fifth or sixth time a year, we assume that they would continue donating at the maximum permissible by the new interdonation interval.

I'm not all that confident that that was a reasonable assumption. The reason I say that, is that we've had experience, significant experience with donors, who take information, particularly deferral information, information that flies in the face of their sense of their own good health.

They take that information very badly, and attitude towards that sort of information ranges from dismay and disbelief, to frank resentment.

The reason why it's important to look at ABO and Rh is summarized in this

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

illustration. On the horizontal axis, we're looking at the years 2000 to 2010, and on the vertical axis, we're looking at the percentage of total red cell usage.

What we did for each one of those years is we pulled distributions of all the Group O and Group A supply to those hospitals, and we took the top ten hospitals. So what we noticed was that in particular, from 2004 onward, it really looks as if there is an insatiable increase in the hospital's appetites for Group O, both Group O Rh-positive and Group Rh-negative.

If I had shown you this histogram exclusively for Group O Rh-negative, the increasing demands over time would be even more dramatic. What is disappointing and dismaying to us, though, is how hospitals have become significantly dismissive of their need for Group A.

When we showed this to our board, which includes hospital representatives, they

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

made the point that this probably reflected a combination of disinterest and laziness on the part of physicians, who found it more convenient to order Group O, rather than to analyze those circumstances where other blood types might be more appropriately ordered.

Against that background, then, and against the background that it is important to analyze by ABO and Rh, let's have a look at the percentages of all the Group A donors, A positive donors, and there were some 55,000 of them last year, and look at each donation frequency.

So this is a curve which is plotted in a cumulative fashion, and along the horizontal axis we've got the frequency of donation. So you can see that the super-donors, the super Group A positive donors, the number that donates six times a year is 0.6 percent. 1.4 percent donate five times a year. 3.3 percent donate four, and then you can see the percentages for the 3, 2 and 1

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

times a year donation.

So the individuals donated 4, 5 and 6 times a year contribute something like five percent to the Group A positive inventory. The super-donors contribute something like five percent to the Group A positive inventory. It will come as no surprise whatsoever, to see that the curve is somewhat different for individuals who are Group O negative.

We have superimposed the Group O negative frequencies in top of that Group A positive frequency, and we're looking here at the 14,684 Group O Rh-negative donors who donated to our inventory last year. By comparison with those Group A positive donors, individuals donating four, five and six times a year make up for something like ten percent of the Group O Rh-negative inventory.

You can see too, recall that the once a year donors in the Group A positive category was something like 66.9 percent.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Fewer Group O Rh-negative donors donate once a year, only 54 percent, and that's because we just drive them to more frequent donation.

There's another way of looking at this. What we can do is look at the percentage's contribution to the inventory by frequency of donation. So now we're looking at the actual units in inventory, as contributed by donors at those different frequencies. It's not a cumulative percentage on the vertical axis on this occasion.

But those individuals donating four times a year, the Group O Rh-negative individuals contribute to 15 percent of the inventory. Something like six percent of the inventory is made up of Group O Rh-negative donors donating five times a year, and probably about nine percent of our O neg inventory in 2010 came from Rh-negative Group O donors donating six times a year, significantly in excess of the individuals who were group A positive, the super-donors there,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

largely because we were discouraging them from donation.

So let's see, then, what the effect would be if we changed the interdonation interval. So we've got percentages on the vertical axis and we've got frequency of donations per year on the horizontal axis, and we're comparing Group A positive, Group O positive and Group O negative.

The first category that we're looking at are those individuals who would be eliminated by a 70-day interdonation interval.

So that means folk who are donating six times a year, provided they continue to donate five times a year. Those individuals would no longer be able to contribute their one donation a year to each of those categories.

You could see that the percentage annual loss, if we change the interdonation interval to 70 days, would be of the order of 1 or 2 percent. So what happens, then, if that interdonation interval is changed to 84

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

days? What would be the donor loss then?

And here's the loss. At that frequency of donation, which now results in two individual donations from the five times a year folk being -- sorry, two donations from the six times a year folk being lost, and one donation from the five time per year folk being lost, we're now looking at significant differences between the Group A pos, O pos and O negative contributions to the inventory.

If we went even one step further and changed that interdonation interval to 112 days, the takeaway message there is that the loss to the Group O Rh-negative inventory at that new interdonation interval would be in excess of ten percent.

A couple of conclusions that we can draw from these observations. Changing use patterns at hospitals certainly have important consequences for recruitment strategies at blood programs. Now, one could argue that those changing use patterns could be changed

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

by physician education. But there's something almost oxymoronic about physician education, and I suspect those changing use patterns could be altered, but I suspect, too, that it will take time.

And then the second conclusion is that lengthening of the interdonation interval will significantly compromise availability of red cells, especially O and Rh-negative units.

And there are similar curves which reveal the effect of a lengthened interdonation interval for Group B donations as well.

So if we do need to look at lengthening that interdonation interval, all I would hope is that whatever that strategy is, it's a strategy that we superimpose after we are confident that we can indeed achieve a lengthening without compromising the availability of the blood supply. And that is my sermon, thanks.

(Applause.)

DR. GORLIN: Merlyn, quick

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

question. Have you actually looked at the increase in the Hispanic -- percentage of Hispanic recipients, simply because there is an elevated Group O in that ethnic group?

DR. SAYERS: You know, we have shamelessly targeted that group for particular recruitment attention, Jed, for the reason that you cite. And, you know, what we haven't looked, but what we could do, though, is look to see what contribution they make at each donation frequency. We could do that.

DR. GLYNN: Jed, you're next. So Dr. Gorlin is the Medical Director of Memorial Blood Centers. He's also Clinical Associate Professor of Pediatrics and Lab Medicine and Pathology at the University of Minnesota, and he currently chairs the AABB Donor Hemoglobin Intra-Organization Task Force, so will provide an update on that. Thank you.

DR. GORLIN: Thank you. I want to thank both the organizers and the AABB for allowing me to work with such an august group.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

The charges for the AABB Committee were to evaluate the existing data on appropriate hemoglobin and hematocrit cutoffs, the donor intervals, what the impact of the new changes would be to either the cutoffs or the intervals, as we've heard today, much paralleling the agenda, serum in measuring iron as well as iron supplementation. I got to work with a large group of experts, many of whom you have heard from during this conference, as well as very productive representatives, as well as AABB staff and consultants.

Because the task is so large, we divided up into groups that closely resembled, again, the agenda of this conference. So a group on eligibility requirements, technical issues including measurement and international practices, what interventions we could make, and some of the other standards, and then collectively looked at what consensus observations we could make.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

It is not lost upon this group that men and women are different, and have different mean hemoglobins, as you've heard about. But one of the challenges of having the same hemoglobin cutoff is that represents the bottom two percent for men, but defers 15 to 20 percent of women, as you've heard, even iron-replete.

So while we all appreciate the simplicity of a single standard, it is, in fact, as you've seen from the NHANES data, about three standard deviations below the mean for males, but only one standard deviation below the mean -- and yes this is venous hemoglobin; it's not finger stick. But it is still a disproportionate cutoff, as we've heard from many of our speakers.

Now, one should not automatically eliminate people beyond two standard deviations. My height is well into two standard deviations above, and Mindy Goldman will point that she's at this end. Now, in my

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

case, I can easily tolerate the fixed amount that we draw, but if Mindy is even more petite, we should be concerned, because in her case it has clinical ramifications.

And, hence, as I think Rich Benjamin has pointed out, deferral should be limited to mitigating risk, either to the donor or to the recipient. I would also point out that even back in the early 1900s, that UConn had a disproportionate number of people both on the men and women's basketball team at the high end?

Now you've also seen, and I think Dr. Illoh has pointed out several times, that the United States and Canada do sort of stand out in having both the single non-gender deferrals, as well as the eight week deferral period. So on this table, you can see that we are somewhat unique in the single standard, and the majority having different gender-specific standards. Many countries have standards of 12 and 13, and there are a number

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

of other countries, in addition to Brazil, as Dr. Illoh has pointed out, that in fact have different male-female frequencies.

Now, you've heard about these large and august blood centers, and so in the spirit of Merlyn's from-the-trenches, in Minnesota, where our women are strong, our men are good-looking, not all of our donors are above average. We would lose, at a cutoff of 13, about additional two percent; at 13.5, additional six percent. If females would cut off to 12, we would actually gain about seven percent, which perhaps means we're maybe not driving double red cells and frequency as high as some other centers.

So what conclusions did the committee make to-date? One, as you have heard from Alan Mast and others, the inevitable result of taking one milligram of iron per mL of blood taken out is that cumulative donations count, and there's donor-related iron depletion. As you've heard from

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

the REDS II RISE study, the magnitude is well-documented.

Benefits. While there's clearly lower rates of cardiac diseases, among others, things among frequent donors, as was shown up by a wonderful article by Leo van de Water, and there's a clearly, healthy donor-confounding effect. So it was not at all clear from our committee's review that there really are clear benefits, clear medical benefits from being borderline iron deficient.

And as we've heard from Alan Mast and others, the adverse effects maybe especially impact young donors.

We've heard, as you've heard today, a review of the NIH and the Indiana blood centers, which you didn't hear today, that was also an iron replacement program for deferred female donors, that at least in the limited pilots, these programs are clearly successful, and as Lou Katz has pointed out, generally if you give iron, the iron level will come up.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Selective standards. There are clearly many factors, including the altitude to moving all our donors to Cusco, Peru, where I actually had the fortune of presenting, and there are actually zero percent donors deferred for hemoglobin in Cusco Peru Regional Hospital Blood Center.

The highest frequency of blood donor iron depletion is in pre-menopausal women, and as Dr. Busch just pointed out, as one designs these trials, it certainly makes sense to be targeting those who would benefit, clearly young and female donors of child-bearing age.

Now, the role of longer donation interval for females, especially pre-meno was discussed, but no consensus was made. Donors deferred for low hemoglobin and hematocrit clearly received very varied information, as Alan Mast just pointed out so eloquently in his article, and there's clearly low-hanging fruit for an opportunity for blood centers to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

collaborate on best practices, though I actually endorse Mike Busch's efforts, that one can do this in a way -- we can actually truly compare informational things, and see which really in fact works best.

In the role of ferritin testing, which donors should it be all, should be just frequent or only those deferred has not been fully explored, and while we very much appreciate the pilot programs done to date, probably we need some additional large-scale testing before any one pathway is endorsed.

We certainly made the same observations, that there's a tremendous coefficient to variation in the various finger stick screening modalities, but perhaps should say but at least pre-donation venous measurements are not very practical in most settings.

We certainly came across the same data, that iron depletion and deficiency are prevalent among frequent donors, and you've

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

heard much more today, that it's even rather prevalent in first-time donors. That iron deficiency signs and symptoms clearly may proceed frank anemia, and waiting for low hemoglobin is probably too little too late.

And as you've heard, the iron replacement programs clearly are feasible in the settings that they were piloted in. We have drafted a preliminary report for the board, but specifically wanted to wait for some of the actually very useful and exciting data that has been shared at this meeting.

But clearly, it is not the role of our committee to changing the CFR or the AABB standards. There are groups for that called the AABB Standards Committee and the FDA, and so it will fall to those groups to make any changes.

I did want to briefly review the O'Meara study, which Joe Kiss did point out for us. Lest we actually think there's harmonization in Europe, I would point out

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

that even though the European standard is 13, 15, 12, 5, that in fact this European Center is using a cutoff of 13.3 and 12.3, okay.

Or, if the ferritin's less than ten, they would then do the counseling by the blood bank physician, and if there was some significant medical concern, obviously they would refer to appropriate medical practice. But then this was -- and they emphasized this was not a randomization. This was purely donor preference, to either extending the interval iron supplementation or dietary adjustment.

And no surprise, those that came back had higher hemoglobins on their next visit, and they obviously had a lower deferral rate. Now they also did say they also had a certain number of people that just didn't come back. So before one extends this just, you know, donor option on a larger scale, one would need to know what that impact of donor loss truly is.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Now the reason for doing modeling, as Dr. Forshee points out, is it's worth understanding the impact, and in this case, the impact might be the Obama jobs program, because if you just do a back of the envelope calculation, at about 20 million donations a year, I could see up to five million people falling into at least the categories of needing physician counseling, which would require about 750 extra transfusion medicine physicians per year.

Obviously, this is facetious. It wouldn't have to be all transfusion medicine.

But understand that as one's trying to scale up such a program, that it would take considerable logistic support, and hence the importance of doing the kind of different modeling that I think Dr. Busch is proposing.

So I rest my case there.

(Applause.)

DR. GLYNN: Thank you. Let me see, time for a break, I guess. So we will take a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

break and reconvene, let's say, at -- why don't we do about 2:40 then, to reconvene here with a panel discussion and Barbara Alving will be moderating that.

(Whereupon, the above-entitled matter went off the record at 2:17 p.m., and reconvened at 2:37 p.m.)

DR. GLYNN: So we are going to please reconvene, and let me see. The panel members, all the speakers from today, if you could step up, I guess, to the podium. Yes, please. So Dr. Alving is going to be our moderator for our panel. Dr. Alving is the former Director of the National Center for Research Resources, which is one of the 27 institutes and centers of NIH, and also a professor of Medicine at the Uniform Services University of the Health Sciences in Bethesda. So I'll let you proceed.

DR. ALVING: Okay. We've got here an extremely dynamic panel, especially considering that it's later in the afternoon.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

But I'm sure they're going to keep us all going. I think that before we begin the panel, I'm to mention to you to be sure to fill out your evaluation sheets, which are at the very end of your packets. I know the organizers will want to see that.

I would like to say that I'm finding this an extraordinarily fascinating meeting. I think a lot has been learned in the ten years since there was once an NHLBI-FDA workshop on maintaining iron balance in women blood donors of child-bearing age. I think you are really now in the pre-contemplative stage, and you're just ready to go get `em, and actually do something.

And I would like to say I'm not sure this is comparative effectiveness research; it's more implementation science, because you don't really have anything standardized, comparing A with B. But that's perhaps just a technicality.

The other technicality I would like

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

to mention is that I think it's really important to think about iron and blood donors as iron replacement and not supplementation. And words count. Over the years, lawyers have taught me that words count, and you're not really supplementing but you're replacing. That makes the big difference. I think that's showing trust and it's showing responsibility that you have to the blood donor, just as a blood donor has responsibility to you.

So, first of all, let's just say -- let's run this a bit like a Quaker meeting to start out. What are some large messages that you can get out in about one minute, each of you? If you could do anything to move this forward, what would you like to do? Then I would have some questions to ask of you.

Let's start with Dr. Sayers, with whom I'm celebrating a ten year anniversary. What would be a message that you'd like to say? You've got NHLBI, they're willing to give you money. You've got the FDA. They

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

want to hear how they should regulate. This is your opportunity.

DR. SAYERS: This is a fantasy, isn't it?

(Laughter.)

DR. SAYERS: Well, what I heard were a number of really intriguing studies which were going to be looking at possible interventions, and I'd like to see the results of those studies.

DR. ALVING: Are you planning to do any?

DR. SAYERS: You now, we're planning to look at ways to iron supplement donors, and what we're strategizing on at the moment is what categories of individuals we would see as best candidates for iron supplementation.

DR. ALVING: Okay. So in thinking about implementing any pilot projects or -- you would like to see careful thoughtfulness about strategies, of where to begin, where the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

best opportunities are at this time, right?

DR. SAYERS: True.

DR. ALVING: Okay. Would you like to see -- I'm hearing lengthening of interval of donation, iron replacement. Do you have any thoughts about one or the other or both or neither?

DR. SAYERS: Are you going to pepper the other ones with questions too?

DR. ALVING: Yes, yes. But I'm just celebrating a ten year anniversary with you, and then we'll go on down the line. You're such a veteran.

DR. SAYERS: I'm really concerned about alterations to the interdonation interval, largely because of what our review of last year revealed, and I don't think we understand the sociology and psychology of altruism enough to be able to predict with confidence that if the interdonation interval is lengthened, we're going to be able to easily make up the number of donors that we're

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

going to have lost.

DR. ALVING: Okay. All right. Dr. Narla.

DR. NARLA: Since I don't really do any real transfusion medicine, but one thing that intrigued me during the last day and a half is this whole biological variability, gender differences as well as racial differences. You know, I think from my perspective, you know, basic science perspective, I think to understand this would be very important in the long run.

We keep talking about how there are differences, but can we really get into, deeply to understanding what the physiological basis is, because I can't believe that men need 15 grams and a woman need 12-1/2 grams optimal oxygen delivery. There must be something regulating these things. The same things with blacks, Black Americans and Caucasians. So to me, there's a very interesting long-term understanding of the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

real basis for these kinds of differences.

And second thing is I think this whole -- since there's so much interest, rightfully so, I think, in iron and iron replacement and iron utilization, even if you're talking about replacement, there are going to be biological variations from individual to individual, in terms of recovery and all.

And again, trying to understand the basis for that, I think, in the long term would be really helpful, you know, in managing these problems.

DR. ALVING: So there are a lot of scientific opportunities to be conducted in parallel with the more practical boots-on-the-ground sort of thing.

DR. NARLA: Yes, absolutely.

DR. ALVING: Okay. There's Dr. Mast there. Is there anything we can do that would encourage you to allow your 16 year-old daughter to donate?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

DR. MAST: I mean the minimum would be a ferritin. I think that would be nice. You know, if I knew she was iron replete and she was okay, then that would be good. But there's so many 16 year-old girls that are not iron replete. I just don't want to do it on a global perspective without knowing what that is. And they're not neurologically developed yet, and so I just think it's really an important issue.

DR. ALVING: Okay, great. We can get into that more. Dr. Forshee, any take-home message, one message?

DR. FORSHEE: I think the main take-home message that I would like to give is that I think it's very important for us to try and get the best possible characterization of what the risks and benefits of any changes would be, and that's part of what we've been trying to do with the modeling approach that I've been taking forward.

We really look forward to working

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

with stakeholders to try and get a better understanding of the range of considerations that need to be included in understanding what the likely implications of any changes are.

DR. ALVING: Okay, excellent. Yes, Dr. Gorlin.

DR. GORLIN: Models are great, all are wrong, but some are useful. Never underestimate the power of sheer empiricism, and blood centers are in the amazing position of having the world's largest clinical trial groups coming to them and we're already sampling their blood on regular occasion.

How can we do it in a way that fulfills our fiduciary duty, both to donor and recipient, to enhance the donor experience, but also to learn as much as possible, how we may further enhance that? I think it is great that there are the studies that are going to happen we've heard about. But what I would love to be able to encourage is multiple centers to try multiple different

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

opportunities, some of which may require variances, including dropping hemoglobins for women to 12, if it's done in a way that protects against further iron deficiency.

I think we need to then have a way that we can compare those outcomes, that we actually learn something about which trials work best.

DR. ALVING: Yes. Please go on, Rich.

DR. BENJAMIN: Well, I'm a great believer in first identifying the problem and then starting with interventions that cost nothing, that have little impact, and then contemplating the more expensive and impactful data. I think we've learned from REDS II that there is a serious issue with iron deficiency, iron depletion, and that it correlates with frequency of donation, and that we should be doing something about the fact that these donors are becoming iron deficient.

The thing that costs nothing is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

better education, number one, and at least recommendation around iron replacement from the donors. If we don't hand them out at the blood drives, at least we can make stronger education and recommendations to our donors.

We see this around pregnancy, around taking folate and around iron. I don't think we're very, very effective as an industry at educating our donors at all about the need to take iron. So that costs very little and we should be doing it now, and I think the AABB should have a role. The CDC, the FDA, et cetera. We should get the message out there that frequent blood donors should be taking care of their iron stores.

Then we get on to the proposed interventions that have serious impact in terms of costs and availability of blood. Those include ferritin measurements and donor deferral. All have much wider implications. I think we need a much higher level of evidence before we even start to implement

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

those changes, and we need to get that evidence in some way that doesn't compromise the blood supply.

So certainly do what's easy and fast now, and put our backs behind it, and study further and get more data on the things that are going to cost down the line, in terms of cash and in terms of resources.

DR. ALVING: Okay. I don't know. I'm 65, I'm getting impatient, but Barbara, let's see what you say.

DR. BRYANT: Well, it seems rather simple. Donors come in and they give us blood, and that's iron. What we're talking about is just replacing their iron that they gave us. They gave us 240 milligrams; we can give them something back that would just replace it, so that they maintain a status quo. So I think it's relatively easy to just approach it from that standpoint.

DR. ALVING: Okay. So it would seem that two of the things to really think

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

about here, or not here, but maybe later, is what is this iron? How can one get it? And it probably ought to be right next to where you give the blood, if you think if it requires extra effort, chances are I just might not do it.

So maybe that's going to lead us into Dr. Keller, who may have some thoughts about iron.

DR. KELLER: Well, firstly, I think we've got a population health problem. Ten percent of young women coming into the blood service are iron deficient. So I think that's where we should start, with some sort of population health program to raise the vision of iron in the community and the importance of iron and iron deficiency, particularly in young women.

So that's, if I had some money, I'd be putting quite a lot of effort into that. But we have done the trial now, and I think that we have a couple of problems. One, that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

we don't have a source of the safest iron preparation in the country. We hope that carbonyl will become available, and we're investigating iron polymaltose, which is just an extraordinary drug, really.

I think ferrous sulfate is available and ferrous gluconate. But I think we're a little bit different to Barbara's situation, which is a more controlled environment, and we have vast spaces and many centers, and we're going to have to have something that's very safe.

So I think we will wheel that out in a targeted way, as soon as we get the preparation. I think interdonation intervals are more difficult, because we have a national blood management system which will not allow us to change interdonation interval at the moment. So we're going to have to negotiate to get that changed.

But I think we need to look at that, as well. I think we ultimately will end

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

up with a combination of the two.

DR. ALVING: Okay. Okay, Dr. Kiss.

DR. KISS: I think a lot of good comments of the panel that you've heard here.

I think -- I have a couple of thoughts. One is that I think our response as an industry of providing care to donors should be proportionate to the harm. I think the harm is a little ill-defined, although clearly we have a duty to inform blood donors of the risks of blood donation and the risk of baseline and subsequent iron deficiency.

So I would support the educational efforts that we have to do. We were just talking before the break, and our blood donor consent mentions you could faint, you could have a hematoma in your arm, you can have nerve damage. But it really doesn't really mention iron deficiency, which is -- you know, it's something missing from what we're supplying to donors.

Over the years, we've tried various

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

efforts, brochures, things like this. I think we do need to create awareness. The proportionate response would be -- and one thing we are studying, and I wanted to mention a point that Dr. Kleinman mentioned earlier, that we've heard a lot of evidence, and we've heard corroborative evidence about donation intervals and deferral and iron deficiency, and clearly they're related. We know that, and I'm a bit -- I'm impressed that the recovery time, even for hemoglobin, let alone iron, the recovery time is longer than that 56 day requirement that was originally proposed.

That was really a normal group of pretty much iron replete individuals, and now we're seeing that recovery time is a lot longer.

That is one of the reasons why we are about to launch this hemoglobin recovery study. Now, it will take two years or so to find the answer. I think we need to do something in the meantime. I think educational efforts. I'm very impressed with

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

the motivation among us to do the comparative effectiveness research, to try different operational modes, because I'm also involved with my blood center, and I know that the operational aspects, the logistics that have been mentioned, in terms of whether we measure ferritins, whether we give, you know, iron tablets out, are -- they need to be worked out.

They need to be worked out well, because what we don't want to do, in the final analysis, is initiate a course of action three or four years from now, instead of saying "did we do anything," well, what did we do? Did we have a call for action, and really not have a plan? So I think it should be proportionate to the problem.

DR. ALVING: Okay. Mike.

DR. BUSCH: A couple of thoughts. I certainly agree with the education and the encouragement to take iron, and I do think we need to better understand the validity of the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

adverse effects of iron depletion. I'm hopeful that in the REDS III program, there's discussion in Phase 2 of launching studies, to really focus on the groups at highest risk, the young donors, the older donors and those so-called super-donors, who we see are becoming iron depleted.

I think those studies need to include, you know, analyses as to the effects of iron depletion on, you know, normal status, et cetera, because we need to really validate that there really is an adverse effect of iron depletion.

In terms of interventions, again, in our organization, what's clear in our management group, one is we need to hear from, to be frank, FDA, that the status quo is not acceptable, that we need to do things that will at least attempt to reduce, mitigate the impact of iron depletion and loss.

Then within our organization, you know, we can do one new thing. We can't do

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

four new things because you've got a computer system and logistics. For us, we have an abbreviated donor history qualification that say, you know, regular donors. We flagged them already and they're qualified. So that's an easy thing to piggyback onto, to target a ferritin monitoring program.

One thing I learned here was that, you know, our thinking was just focused on those low hemoglobin donors who are frequent. But I think we also need to pay attention to the hemoglobin levels in the donors who have higher hemoglobin, and what we saw from Tony's work, that the change in hemoglobin should be monitored, and donors who show evidence of actually, you know, evolving anemia clearly need to be monitored and assessed for iron depletion.

So I'm excited about the opportunity to do these studies. But I think it's going to require both some focus, you know, probably NIH-funded studies and then

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

working together to figure out how to, in a phased way, implement some modifications and then know at the end whether, which works and which doesn't.

DR. ALVING: Okay. So questions from the audience. They're right here. Shoot them some hard ones. Anybody? Okay. Here comes a big gun. I see this.

(Laughter.)

PARTICIPANT: Big gun, soft question for Dr. Keller. So you commented very briefly about the prior study of donor education. You know, we're leaning here towards some sense that, well, that's something we can do now. But was it not the Australian experience that counseling donors didn't work, you know, when you encouraged them to eat iron-rich food? Can you just clarify whether they were also encouraged to take iron?

DR. KELLER: Yes. Did the counseling work? Well, we don't really know. We instituted it, but we didn't really, you

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

know, dietary advice, et cetera, if you were near the hemoglobin threshold. That happened at, during the donation process, the interview process.

But we didn't really monitor the results, and we didn't give them advice about taking external iron. We concentrated on diet at that stage, because it was a simple thing to do.

DR. ALVING: What has been your impression now, since you're done the studies, I mean in terms of your donor response? Can you tell any difference? Do they seem to appreciate the fact that you've educated them about iron and actually give them iron? Do they want to continue taking it?

DR. KELLER: Well, when we asked them. I mean we asked them a direct question. Would you consider taking iron after the blood donation for eight weeks, and 87 percent of those people said yes, and 79 percent of the placebo group said yes as well.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So I think there's good compliance. But that's specifically related to carbonyl iron, I think. I don't think you can transfer that to other iron ---

DR. ALVING: Right. Now could you say a couple more words about the other iron that you're using, or that you want to use?

DR. KELLER: Well, I don't know a huge amount about it. I know it's available as an intravenous preparation. I'm not sure whether it is here, but it is in Europe, and there are now all preparations, and there are articles that I can make available.

But in talking about the safety, it's got a very high safety profile from the child overdose point of view, or adult dose overview. It's absorbed. Nothing really interferes with its absorption at all. So it can be achlorhydric, or you can take all those inhibitors and they don't interfere. So it seems to make sense, and very low side effects as well. So it seems manna from heaven,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

really.

DR. ALVING: Harvey Klein, do you know something about this? Okay. Can you just come up and say anything that you know? I mean everybody may know this. But it's just good to -

DR. KLIEN: HH Just a couple of points. Carboxymaltose is licensed in the U.S. for intravenous use. There is no oral preparation in the U.S. It is certainly touted as being a safer iron preparation for intravenous use. However, much less of it has been used in many other intravenous iron preparations, and I suggest to you that when they've gotten a couple of million doses used, we'll have a better idea about the safety profile. I just don't think we have an idea about the safety profile.

I think the same is also true about the oral preparations, and we'll see if that's the same for this one. One other point that I don't think is really made, but I think many

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

people here probably know, that the GI toxicity from iron is generally related to the amount of iron available for absorption.

So that maybe the difference between ferrous sulfate and ferrous gluconate is really not the gluconate. It's the amount of iron that you get into your stomach, and less with the gluconate.

DR. ALVING: It's interesting that Gary Brittenham, in his earlier studies, and then that's more than ten years ago, I think, used about 100 milligrams of carbonyl iron, and you used about 40, 45, and there was -- what was your reason for choosing that dose, rather than maybe what had been used in other studies?

DR. KELLER: It was basically Doc Newman's study of 2006, where he said that 40 milligrams of carbonyl iron for eight weeks would do the trick. So we thought we'd use the lowest dose possible, so that we would reduce the side effects.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

DR. ALVING: And you're happy with that dose?

DR. KELLER: Well, we haven't tried any other doses --

DR. ALVING: You were sufficiently --

DR. KELLER: But yes, we didn't have any problems with that dose.

DR. ALVING: Okay, Rick.

DR. DAVEY: Yes. I think Joe, you mentioned that you didn't think you informed donors about the risks of iron deficiency. Now that's an important point. We've heard a lot about the potential risk of iron loss in blood donors.

I'm curious amongst the panel members, what if anything do you do to inform donors about this risk? Informed consent, education materials, whatever, or nothing? I'm kind of curious.

DR. BENJAMIN: We do have an information pamphlet for donors that are

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

deferred for low hemoglobin, and they're all very much along the lines of, you know, eat the right foods and go have your spinach, which you know, I don't think that's a very effective way of educating donors at all.

When I talk about education, I think we need a far more national-based higher profile. We need to get it on the news, that you know, frequent blood donors need to worry about their iron. So two different levels of education. I don't think what we're currently doing is very effective at all.

DR. ALVING: Okay. We've got to make -- oh yes, go ahead. Jed.

DR. GORLIN: I do share some of Richard's frustration. I, a decade ago, started the total care of the donor program. When one has a blood center within eyeshot of General Mills, I got them to donate 5,000 boxes of Total Cereal, which is 100 percent of your daily iron requirement, and if you were deferred, we gave you a box of the cereal, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

a brochure that basically was the WIC iron brochure, rewritten to be more generic. I was very proud of the program. The medical director of General Mills retired and that was the end of the program.

But in fact, we did not do any quantitative studies, and I have no objective data to suggest that it in fact had any effect on subsequent donor deferral rates, et cetera.

So it was a wonderful example of well-intended low-hanging fruit, but without any objective measures and without even any subjective impression. I think we need a more infrastructure supported program if you're really going to have a donor educational program. Just handing out a brochure doesn't work.

DR. ALVING: Yes. Let's see. Dr. Mast, were you going to say something?

DR. MAST: So I just want to -- I don't know if it works or not, but we did develop a, hopefully a new and improved

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

brochure, based on the Blood Center of Wisconsin's previous "eat ham and broccoli and come back and try again to donate tomorrow" brochure. So in developing this, we had community medicine, physicians and a health, how do you call it health education expert, Arlene Fink from UCLA, that helped us develop this, and we did the very best that we could.

Took it to a focus group, and then saw all the problems with it. Came back and redid it again, took it to another focus group and published it in *Transfusion*. So it's a supplement. So I think it's okay.

Again, we have no evidence that it works or not, but I think it's good for people to know out there we put a lot of work and effort into it, and I think it would be a starting place that people might want to --

If you're looking for something educational besides eat food and come back and try and donate tomorrow, I think this would be a good thing. It describes all the types of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

anemia and does describe iron deficiency and how you need to take iron pills, not just --

DR. ALVING: Is there a way you could get that up on a website or something, so everybody could --

DR. MAST: So it is on the website. If you search for -- it's Stacy Young, Y-O-U-N-G is the first author, and I'm on it also, and it's in *Transfusion*, a supplement online to that paper is the handout. There's no copyright or anything. I'd be happy if anyone wanted to use that.

DR. ALVING: Is there open access, because I think the *Journal of Transfusion* doesn't have open access. I think we're not linked in with the libraries. Is that the case? Yes.

DR. MAST: You can have after a year.

DR. ALVING: After a year, okay. That's another thing to think about. But that's another meeting.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

DR. MAST: --last year, I'm pretty sure. So it should be available. If not, I can send it to anyone.

DR. ALVING: Send around the link in some way right, or post it or do something, so we can all take a look at it. That could be very useful. Okay. Let's get some of these, then we'll come back to Doctor -- sorry.

DR. NEWMAN: I want to just thank Dr. Mast, because and the American Red Cross.

We have -- the physicians in the American Red Cross have looked at your brochure, and we agree that it's very helpful, and in fact we have revised the letter that we give to donors, donors deferred for hemoglobin, incorporating much of the advice that you developed for that brochure.

So it is available; it's very well-presented. The American Red Cross physicians reviewed it, and it did lead to a revision of our hemoglobin deferral letter, so thank you.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

DR. MAST: That's encouraging to hear. Thank you.

DR. ALVING: Good. So if you could send the link around or the reference, that would be great. Let's get -- is it Dr. Newman?

DR. BRYANT: Okay, Bruce Newman, Red Cross. So there's been a lot of emphasis on the frequent donor, and yet the first time pre-menopausal woman that comes to us, according to the data from CDC, there's about 12 percent iron deficiency or iron-depleted, and half of them won't pass our hemoglobin, but half of them, or six percent, will, and so that's --

Then after their donation, they're even more depleted. So it's an important issue. So how do you feel about that?

DR. BRYANT: Well, in the NIH program, we did treat those donors that came, that if you didn't pass finger stick hemoglobin you were given iron. A lot of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

those were first-time donors, and they were young females.

We really felt there was no harm in giving iron to a group of donors that are iron deficient. They came back, and we were able then to look at their hemoglobin and other lab values, and you know, it was interesting.

About 40 percent of the women that we did give iron to with low finger stick hemoglobins, had to take iron a couple of times before their hemoglobin got to the point where they could donate blood.

But then they were part of that group, that continued to be able to donate blood. We got more productive donor visits per year per donor, and they continued the iron. Their ferritin went up and it handled the blood donation and restored their stores, our stores.

DR. ALVING: Okay. Let me just get Dr. Sayers, then Dr. Kiss.

DR. SAYERS: Well, I wanted to get

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

back to something that Jed said before I forget it, and he was talking about iron fortification of foodstuffs. Ken Finch's iron labs were mentioned a little earlier. One of the things that Ken was interested in was iron availability.

What emerged during his studies was that iron fortification of foodstuffs that were cereal-based was ineffective because the cereals bound the iron, and it doesn't matter to what extent you fortify a cereal. You're not going to have any of that iron available.

So any benefit from, I don't want to discourage the cereal eaters here. I mean any benefit to one's iron balance is totally illusory.

DR. KISS: I just wanted to amplify on that point too, is that another thing is how many, you know, how many of our donors, present company included, have GERD or reflux and take acid blockers.

So there are also very commonly

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

agents that donors are taking, individuals are taking, that block iron absorption, which compound the problem, in addition to the bioavailability of food.

So the one myth is that, you know, non-heme iron is absorbed, and as it's been said, it's an old joke, but you know how Popeye got his iron? It wasn't the spinach; it's because he ate the can. It was more bioavailable.

(Laughter.)

DR. ALVING: All right, okay.

DR. CABLE: Just on diet, it's not all that prominent in the RISE publication, the first publication, the enrollment. But we looked very -- well not as carefully as a diet expert would like, because that was a 30-minute interview or something.

But we did ask a whole page worth of questions on how often you eat the following iron-rich foods, and there were eight or nine categories of foods, including

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

oysters, which I didn't know were iron-rich, but it turns out they are. Shellfish, oysters, which I like, so that's good.

But when you looked at the odds ratios in, you know, 24 and 25 donors, for the relationship to iron status, there just wasn't a hint that diet of the donors had anything to do with their iron status.

I mean it was so negative that it wasn't even almost worth putting it in elaborate detail in the paper. So there is an appendix, I believe, online that you can get, that shows the individual odds ratios for the individual food categories.

But my assessment from all of this is that any kind of dietary or nutritional counseling will just be eyewash, and make us all feel good, make the donors feel good, and maybe donors should be eating well anyways.

But the last I knew about all this was as long as you're eating a reasonable caloric intake, and even if you're a strict

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

vegetarian, apparently, because that was included, you're going to get enough iron. You're going to get all the iron you're going to get from your diet, and what really we have to look to for the extra iron is medicinal, whether we like it or not.

So that's very clear evidence in the RISE study. Now granted, we maybe weren't powered to see very small differences, but we're talking about a lot of iron deficiency here, and I don't think we're going to correct it with anything but the can, as Joe said.

DR. ALVING: Yes. You want to make a comment?

PARTICIPANT: I'm about to wildly switch directions and topic, so if you guys have other relevant conversation. I'm just wondering, this is for Dr. Forshee, what your planning in terms of validating some of the compartmental models you're coming up with?

DR. FORSHEE: I'm sorry. You're asking about validation of the models?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

PARTICIPANT: Yes.

DR. FORSHEE: We've already started doing some internal validation to be sure that when we put in parameters that are similar to the current number of donors that we see, that we're getting out something approximating the current number of donations.

The model currently isn't far off that. If we put in about 9.9 million donors, we're predicting somewhere in the range of 15-1/2 million donations per year under the current parameters. So that's some of the internal validation that we've been doing.

Ideally, it would be great if we could take the data that we have, and see if the model structure would predict some other external data that wasn't used to do that. We haven't identified such an external data set yet, but that is -- that's something that we'd be very interested in doing, in terms of validation.

DR. LEITMAN: Hi Barbara.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

DR. ALVING: Hi.

DR. LEITMAN: I remember really well that discussion with a bunch of blood center experts ten years ago at the consensus conference, where a huge amount of data was presented, similar to data presented in the last two days, except it wasn't a big multi-center study, that blood donation is a problem in terms of iron deficiency in donors.

Every single one of the center directors, blood center directors, ended with I cannot give iron to a donor, basically because my medical-legal experts tell me that I can't do that. It's nice to hear that that is minimally mentioned in the last two days.

But I'm concerned that ten years from now, we won't be at the place we want to be, because ten years after the meeting in 2000, there are very, very few centers, a tiny number, that mitigate in any way by trying to replace iron.

One anecdote. Before the NIH iron

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

study was started, the convention in the blood bank at the NIH was to give a script to each subject who did not pass their hemoglobin, and tell them to take it to the NIH pharmacy and get iron for free.

Now we could follow that, and there was education that accompanied that. We could follow that by asking the pharmacy how many scrips for iron they had filled. It was less than ten percent, maybe even less than five percent were filled.

It was free, it was only down the long corridor. It was maybe a 20 minute wait, but someone, maybe it was Ritch Cable, said if you make it in any way inconvenient, even minimal inconvenience, it's not going to happen. I think Merlyn said educating physicians is an oxymoron, and we can say that because we're physicians and we can poke fun at ourselves.

But educating donors is very difficult, and I don't think that the most

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

well-written brochure or letter is going to do the trick. I don't think there's anything that we can do but to give the tablets to the donor. If you think it's a problem, that is the most efficacious way to get iron into donors.

DR. ALVING: So this is, I think, an engineering problem, and I think it's a business problem. I would love to see some pilots where you say what is the most cost-effective way to do a pilot of iron replacement.

The NIH has spent gazillions of dollars for these clinical and translational science awards -- have to get that in, it's habit -- to take research into clinical area and out into, whoa, the community, to benefit patients, and you are the ideal people to do it.

I've always considered the blood center community as being the most organized in, you know, if you think of all the efforts

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

in medicine, I mean you're organized to catch errors. You do tremendous amounts of things.

You're highly disciplined. But how could you, as a business model, maybe working with a business school, get this implemented?

I certainly agree with Susan, that you have -- a woman, a donor, man or woman, has to be handed it in the hand, because there are so many iron preparations out there, et cetera, et cetera, and it shows you really, really, really do care.

I think the women, medicine expectations are much different now, even from ten years ago. If you look at our clinical trials, ethics, a huge part of it. So what is the ethical aspect of treating, not treating, not putting this into your -- you have a consent form. That means you have to inform, and you're not informing basically. You're hiding under a bushel.

I think you're going to find that donors would be very appreciative. It shows

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

that they trust you, you're going to take care of them, and I know you're saying you're not doctors, but you're doctors enough to take all their blood and all their iron stores, if they're a woman.

So you know, we've got to make Dr. Mast willing to have his daughter give blood.

The other thing is the -- you've got, the FDA has a problem here. So you've got this BPAC Committee, and they've all voted unanimously to raise the hemoglobin level for donors.

However, I know they are advisory.

But then you've got to go back to them. So that's going to be interesting.

PARTICIPANT: Well, I think part of the issue is that -- well, first of all the donor, BPAC is advisory. We generally follow the advice. If we don't, we need a good rationale, et cetera, et cetera. But I think the problem that we faced was looking at the issue in compartments.

It's very clear that if we simply

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

look at changing into donation intervals, we run the risk of tremendous disruption of the blood system, particularly blood groups, and racial diversity, et cetera.

We can't really disassociate that, I don't think, from the problem of monitoring and managing iron in the donor. I think if we do the two things together, then more flexible strategies become possible.

I think that that's sort of the way out of the box with these conflicting recommendations from the BPAC. In other words, we can't just reduce the blood supply by raising male hemoglobin threshold, if we don't find compensatory mechanisms.

I think that's clear, you know, and we understand that. So I think that what's needed here is the integrated approach, and that's what we're reaching for. We need a strategy to monitor and manage the iron store in the donor. That will create the opportunity potentially to change thresholds,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

to change interdonation intervals.

I think the challenge that we're then presented is is it a one-size-fits-all policy, you know, male 4x, females 3x. Well, we know that that may help on average, but it may also have unintended consequences, as Dr. Benjamin pointed out.

So I think ultimately the challenge that we're getting into is whether to have uniform policies, or to move toward what we like to call in the 21st century, individualized care, and I think that that's the bigger of the two challenges.

You know, there's taking on the challenge of iron management, and doing, you know, the greatest good for the greatest number, and what lies beyond that is strategies that treat each donor as an individual, and I think that that's harder yet, but it should be our ultimate goal.

So I think there is a way to understand the advice from the BPAC, putting

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

aside the whole issue of how, you know, capillary hemoglobins may actually be compensating. I mean we heard this very clearly. At high hemoglobins, you're underestimating venous hemoglobins, so we're probably only accepting donors with higher venous hemoglobin if they're males.

Conversely, at lower hemoglobin, we're overestimating the hemoglobin. So we're probably accepting venous hemoglobins that are lower in females. So it's sort of perverse, but we're probably already doing what we sort of wanted to do. But what lies beyond that is the harm that we're doing, ignoring the iron status.

My simple answer, I guess that was a little wordy, was we have to put the two things together, and that's what will create better options for public health and donors.

DR. ALVING: So it sounds like sort of a strategic plan or a developmental plan going forward, taking these things into

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

consideration. And actually, I think, as you've mentioned, this is a public health issue. You're going to go beyond the blood community, and that's good. That's a good thing.

Okay. So you've got all of these different recommendations among all of these countries. Have you in the United States, have we in the United States benchmarked against them, and if you look at, is there, are there data out there in terms of donor deferrals, shortage of blood supply?

I mean does the U.S. do quite well, thank you very much, with what is already in place? You know, do you feel a big need to be more like France or more like Brazil or whatever? I'm not talking economically, but I mean, you know, Canada, Switzerland and the U.S. are kind of hanging out there.

But are you happy enough with what you have if you do your benchmarking?

DR. SAYERS: Barbara, very

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

difficult to be confronted with a question to a Texan, would you like to be more like France.

(Laughter.)

DR. SAYERS: I think one of the challenges, because we have looked at benchmarking, one of the challenges is that when we look at what the National Blood Supply demands are here, I mean it's very obvious that we're pursuing to the grave individuals who in other parts of the world would not be transfused.

So the benchmarking is rendered difficult by virtue of the fact that we transfuse more by comparison with how much we draw than do other countries, where we would like to draw comparisons with our practice and theirs. So it's a challenge. It's not impossible, but it's a challenge, benchmarking appropriately.

DR. ALVING: Okay. Anybody want to add to that?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

DR. BENJAMIN: Just to add numbers to that, France uses 32 units of red cells per thousand. The U.S. uses closer to 50. So we're clearly using a whole lot more blood than they are. So it is difficult to benchmark, and the UK and Australia are also on the lower side.

Although there are some groups, such as the Alliance of Blood Operators, that we get together and talk with our UK colleagues and Australian colleagues, and we do a certain amount of benchmarking and looking at things.

I'm not sure we've actually looked at iron depletion, but that's certainly something we could do.

DR. ALVING: Or I'm thinking about donor deferrals, for example. Do you have about the same rate of donor deferrals among the countries, or I don't know if you've --

DR. BENJAMIN: That has been benchmarked. Off the top of my head, I can't

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

remember exactly.

DR. ALVING: But we're not really that much different. I guess you'd say probably the most blood is transfused what, in the last few years of life, of someone's life, just like everything else?

DR. BENJAMIN: Sixty percent of our red cells are used by folks over the age of 65. As we know, that's the population that's going to grow by, you know, just under 50 percent in the next 20 years. So we're in for a rough time with the baby boom with that statistic.

DR. ALVING: Okay, all right. Are there any other -- okay, Dr. Cable.

DR. CABLE: Just a couple. Speaking of Alan's daughter, and she's a very attractive girl, by the way, none of the studies studying iron stores of blood donors or iron supplementation in blood donors studied donors under 18, neither RISE.

We hope to fix that with a study of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

16 and 17 year-olds. But just a couple of anecdotes about the teenage donors. One is that at a blood-donor, blood-sponsor recognition dinner I went to in a southern state I don't need to name, two high schools got an award for having 40 graduating seniors with one gallon pins, which pretty much knocked me off my seat. I'm realizing that this is related to my second point. So teenagers are one point.

The second point is I'm retired from operating a blood center, and as I was retiring, double red cells in high schools were starting to become popular, and I told my recruiters that they could put double red cells in high schools over my dead body, and they were about to say they could arrange that.

(Laughter.)

DR. CABLE: When I retired, I wasn't retired a week before those double red cells weren't rolling into the high schools to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

the unsuspecting teenagers of Connecticut. Now, and we only allow 17 year-olds in Connecticut. We don't have the 16 year-old issue.

I also observed in the last year or two of my operating career, the wholesale movement of the blood industry to bleeding 16 year-olds is perfectly safe. We don't need any data. Oh, we need a lot of data to stop bleeding people, but we needed no data to start bleeding 16 year-olds.

So Alan, the iron expert, is advising his friends, don't give that often. The head of the National Red Cross' Medical Department saying that the recruiters are attacking high schools and colleges, and I think I quoted him right, and a couple of other people doing the presentations said they couldn't convince their center to go along with some idea they had.

There is a cultural -- I think I need to say this. There is a serious cultural

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

problem in the blood industry, that the donors' interests are not being put first. It's ethically wrong, and it's going to get the industry in a whole boatload of trouble, and I think you alluded to it.

I thought I needed to kind of call the audience out, that we really need to put donor advocates, and they used to be physicians. I'm not sure they are anymore, but somebody needs to be saying, wait a minute. Because the recruiters have only one role: get to goal, and they have incentive compensation now. Think of the bankers.

It's not a good system, and we ought to let's just know that, and trying to change that system, I mean I've gotten hate mail already for my role in RISE, it's going to be tough, because the system isn't going to want to change, because blood has become commoditized, and efficiency and cost are important parameters.

We can get blood; it just costs

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

more. But that's an obscene concept in many blood centers today, and we're going to have to operate in that culture. I'm hoping somebody here could think of ways to change the culture, as well as the practice. With that, I'm done with my sermon now, I'm sorry.

(Applause.)

DR. ALVING: I would say, you know, we have to get out in front of it, before it gets out in front of us, and all you need are some teenagers to go online on Facebook and that does it in. I mean, you know, we do any clinical research protocols with 16 year-olds and mom and dad have to sign. I know. They have to sign permission for blood donation, but do they really know what they are signing for their child do to?

So I'm going to come back to Dr. Mast with a question. What are you doing at Wisconsin Blood Center? I mean you've got an R01, you've gotten money for all this good stuff. You've got my dear friend Gil White.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So how are you saving the world up there in Milwaukee?

DR. MAST: I just go to work every day and try to do my best.

DR. ALVING: Not good enough.

DR. MAST: Yes. It is hard. I'm going to go back and we'll talk to our marketing people, and see what we can do. They'll give me lip service and be nice to me when I'm there, but I don't know if they make any changes once I'm gone. Does that make sense?

So it's sort of building enough -- you know, I think we'll go back and I'll discuss what happened, and then we'll see, you know, a couple of ideas about what we can try and do and convince them, and we're doing the STRIDE study, which I think -- you know, it just takes time though. You know, it takes a long time to enroll all those donors.

So that's all we can do. I can just try talking to them. But like I said,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

all I have is an M.D. and a Ph.D. degree. I don't have a business degree or a marketing degree, so I'm not the final say.

DR. ALVING: Okay. So it would seem that coming out of this is going to be a series of possible studies, that there's actually going to be some implementation studies that will be undertaken, considered, and some will be taken together. There will be multi-site studies and some will be other kinds of studies.

I mean if you do something at the blood centers, are you going to do anything on your own? Are any going to do on your own or are you going to do it as an industry? What are some of the approaches you're thinking about?

DR. BRYANT: The NIH adopted iron replacement as part of standard of care after we finished this protocol, and donors that have been identified on the iron replacement protocol continue to receive iron when they

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

donate blood. Also, donors who have hemoglobins of less than 12.5 are given the option to have blood, I mean, to have iron.

And that's what we continue to do at the NIH, and it's successful.

DR. ALVING: But people will say NIH is on another planet. You're not the real world. So that's the issue.

DR. BRYANT: Right, and we've talked about, you know, could it be that you're talking about a business model? I mean would this com down to having a volunteer in the donor room, in the canteen area where the cookies are served, and handing out iron, you know.

You've just donated a unit of blood, you've lost some iron. Would you be interested in taking this? If you don't have a volunteer that can do this, put that on your big TV screen. Everybody's into the --

DR. ALVING: They could be educated while they're giving their blood, yes.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

DR. BRYANT: Yes, a YouTube thing.

But anyway, to get the information across and make it available.

DR. ALVING: Yes.

DR. BRYANT: Like Tony said, there were people -- when asked, they seem to be interested. Eighty-seven percent seem to be interested in taking iron replacement.

DR. ALVING: Okay. Yes.

MS. BAGSHAW: Kathleen Bagshaw, Children's Hospital, and I'm a worker bee. I'm a QA and I also screen donors and defer donors and counsel donors, and I would ask the doctors who were very much an active part of their protocols, who actually spoke with donors or who were one-on-one with some of them, what was the retention that you saw, when you had a very personal interaction with, especially new donors who were being deferred and then you counseled them on what they could do to come back and donate the next time?

And let me add this. I can tell

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

you that we have a savvy population out there for the most part, and I've seen young women who put themselves on a longer deferral so that their hemoglobin can come back up, who eat the steak and liver before they come through the door, and also seen the male donors who, at 54, with a 13 hemoglobin, were deferred by their personal physicians for a decline in their ferritin levels.

So but, really my intent here is to say, do you see a demonstrable return of donors when you do this one-on-one counseling? Thank you.

DR. BRYANT: Absolutely. I started this study as part of a fellowship project, research project, and I saw every single donor and counseled them in the early, probably the first year and a half of this study. In talking with donors and explaining the situation, and that, you know, we're going to run these labs. Then I would call them with their results and explain to them. These are

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

your iron stores. Your ferritin is a single digit, you know. This is what we can do. This is what the iron will do. We had a huge amount of donors buying into this.

They were excited about the fact that somebody actually took the time to explain to them why they were being deferred, and what could be done about it, instead of saying, oh well, just come back at a later time.

They were excited about taking the iron. Many felt better, and I would get -- I mean this is so hard to quantitate and put in a paper, when all of the sudden donors are saying I'm not falling asleep at work at 2:00 in the afternoon.

I had a donor walk in and say I've lost 20 pounds on iron. Had nothing to do directly with the iron, but they actually had enough energy when they got home to go to the gym where they had membership.

I got phone calls from spouses

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

saying that their marriage had improved, which is too much information.

(Laughter.)

DR. ALVING: I'll be giving these out back at the back door.

DR. BRYANT: But donors loved me. I was extremely popular. Susan Leitman used to laugh about how going to the cafeteria to eat with me was a big ordeal, because people were stopping me in the hall and hugging me, you know, and as Texans, they don't do that a lot up here. But in Texas, it's well-received.

But, so taking iron made them feel better. They were happier about it. I got to where I had donors calling, and see this is a great way to remind donors when to come back when you run out of tablets. It's time to go back. I mean it's even better than telerecruiting.

So they would come back and say, you know, I have to come in tomorrow, I'm out

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

of iron, and I would have assure them. It's okay, you can miss a day or two. They didn't want to miss a day or two.

They felt good on the iron. They were able to donate, they were happy, they felt like they were doing good for patients. So it was such a positive experience in the donors that took iron. It was certainly a win-win.

DR. ALVING: I think on that note, but I take your point. I mean the women who are donating are often mothers. They've got a full-time job. They're trying to hold it all together, and we've got to make sure they've got a full tank of iron. Okay.

DR. BRYANT: Iron is good.

DR. ALVING: Now, let's say with that, I think we've heard some very clear things. Ferritin seems like a great idea when you're going to monitor for iron, and you've put forth some very good protocols, and we're going to then have a wrap-up after that. So

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

I'd like to thank all of you for your comments.

(Applause.)

DR. DAVEY: Okay. For those of you who have hung on through the two days, appreciate it. It's been a great two days. We're going to have a brief wrap-up now with the moderators of the three panels who we've had, two panels yesterday and a panel today.

So I think Jed's stepped out for just a minute, but Harvey Klein and Barbara are here. What we'd like to do is just see if we can find some overarching thoughts, conclusions, maybe some steps for the past forward, from what we've heard at the three sessions that we've had. Even though we're not looking for specific recommendations to the FDA. If you have any, we'll be happy to listen to them, and I know that the three sessions, certainly we don't want to look at it all as silos.

We've heard a lot of the overlap

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

between hemoglobin, iron, iron replacement, ferritin, measurement of hemoglobin. These are not separate issues. So even though I've asked the moderators to give maybe a brief ten-minute summary of their panels, certainly any interaction between the three are welcome.

So any concluding thoughts, recommendations, steps forward, research opportunities that you would like to share with us from your groups, I'd appreciate that. Jed, Harvey, come on up.

DR. KLEIN: Thank you, Rick. Well, we've certainly heard a lot of new data over the last 48 hours. It's going to be difficult, I think, for the regulatory agency to get enough of a handle on these data to make regulatory decisions. I'd be interested to see how they're going to do that. I think it's clear that we use a poor screening test for donor health. We don't know much about donor health. We haven't followed up donor health very well in the past, so we haven't really identified the problem very well. Yet

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

we have a system that generally works.

It's not necessarily evidence-based, and it's not necessarily the best system, and in fact it's a system that has changed a little around the edges in the last 30 years, but it really hasn't changed very much, despite new technologies, new tests, disruptive technologies that could change the way the system works.

So with that, I think I'd like to ask our -- Jed, I think, why don't you have a seat on the panel, and I think you're going to lead off, to give us a little summary of the hemoglobin standards for blood donors in the United States.

DR. GORLIN: So I thought I -- I couldn't find Ritch Cable's father's tie on my ancient version of PowerPoints. I thought I had a little fireworks. We actually heard Dr. Illoh, who summarized the current standards, and I thought it did an eloquent job of setting up the challenges we face.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

I agree with Dr. Epstein, that blood centers like the FDA tries to avoid compartment syndrome at all times. We heard that in fact many other countries do successfully use gender-based standards, do use 12, 13 or other hemoglobin standards, and do use different intervals, although as Rich pointed out, often at a lower red cell per thousand population consumption.

We heard her discuss some of the challenges faced by the BPAC suggestions, and clearly the objectives of this meeting were to address some of those challenges. We heard a lot of data from Dr. Spencer, summarizing the data on hemoglobin distribution, deferral in iron measurement, and I think helped objectify some of the definitions.

To the extent that future research could at least agree on some common definitions of iron-replete, iron deficient erythropoiesis and absent iron stores will allow us to compare study versus study.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

I think one of the points was we have met the enemy and they is us. Clearly, there's a dramatic increase in iron deficiency among repeat donors than first-time donors. We've also heard from Bruce Newman that there's a significant amount of iron deficiency in first-time donors, and we have a responsibility to them as well.

Even if finger stick hemoglobin overestimates venous levels at low levels, we still have a cutoff that is, you know, way high for a third or a quarter of the women, and certainly well below the two standard deviations for men.

We saw that it's taking longer than the eight weeks to replace -- to fully reequilibrate the hemoglobin level, and it's really only at about a half year that comes completely back to baseline. On the other hand, the impact is of making changes to hemoglobin, of either 13 or 13-1/2, would not be small. It is of interest that the RISE

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

data was somewhat higher than the multiple blood centers that have presented. But still, those impacts are really quite substantial at the 13-1/2 level, and as Merlyn pointed out, that impact on O negative is obviously a much bigger deal than some of the other blood types.

Dr. Forshee had some elegant modeling, compartment syndrome notwithstanding, that in fact demonstrate the interaction between donor interval and hemoglobin cutoffs, and those, I think as we start pilot experiments, will be specifically important to actually track.

I think we heard elegantly from Rich that an evidence-based system would be appreciated. At the same time, we also saw the data shared from Barbara Bryant, that in fact dropping that hemoglobin cutoff of 12 to 12-point, 12.5 to 12.0, does not in fact dramatically increase the percentage of iron deficient, and that actually going to 12, 13,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

a gender-based thing, would actually have really minimal impact in at least Ann Eders and others' data, my own centers included. That anything that involves reacting by drawing donors even more frequently is -- or larger volumes from donors, as Rich has pointed out, really impacts disproportionately our young donors, and is an unintended consequence we need to certainly watch out for carefully.

We heard a number of reasons why a changing interdonation interval may have some negative impact, and in educating donors on iron replacement, we've just had, I think, had wonderful input from the panel discussion, why simple education is not so simple.

The opportunity to have an iron replacement program to replace losses certainly is attractive, but having some mechanism to actually hand the donor the iron, may in fact improve outcome. Changing criteria immediately may in fact take away the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

option of really learning about multiple different options that would combine approaches, that in fact may have the most synergistic effect.

We heard from Toby Simon that the plasma industry in fact has, by drawing the donor testing out of the concurrent plasma, in fact avoids any chronic, significant chronic depletion of iron, and it's certainly tempting for our platelet donors, why we couldn't do the same? One wonders actually for our platelet donors, as well as their plasma donors, ought the donor eligibility hemoglobin requirements be absolutely the same as whole blood. Maybe medically they shouldn't be, if chronic iron loss could be addressed.

We head from Lou Katz on the impact on at least his platelet pheresis donors maybe is of the same order of magnitude as whole blood, and that's particularly significant when their TRALI compliance strategy is to increase male donations.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

So the numbers on red cells were nine and four. The numbers on platelet pheresis donors were even higher, 12 or 13 and 6 for the 13 and -- 30.5 and 13 cutoffs, respectively. From the panel discussion, I thought I heard the consensus that double red cell eligibility may already be accounted for by the higher cutoff and longer deferral, and the larger donor size, but I'm not sure that that was the message I heard today, and it's probably worthy of further discussion.

But clearly some European countries use concurrent venous hemoglobin for retrospective donor qualification, that donor counseling programs include contacting males for less than 12-1/2 and females for hemoglobins less than 11. But the disturbing message from Mindy Goldman was that only about half actually heed the advice.

Should the platelet and plasma cutoff be the same as whole blood, and how to translate recovery time into an appropriate

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

deferral interval? Those two may not be the same. I did not hear anyone advocating immediate changes. I think there was a consensus that the pilot trials of various interventions would facilitate recommendations.

In the REDS III, STRIDE and 50K program in the United Kingdom, clearly will be great steps towards assessing possible improvements. But I would argue that they should only be the start, and that should not dissuade other and equally creative options, and that finishes me in under ten minutes.

DR. KLEIN: Thank you, Jed. Are there any other comments on this particular area that people want to add to the summary that Jed gave about hemoglobin standards?

(No response.)

DR. KLEIN: If not, thank you Jed, and we'll move on now to the measurement of hemoglobin and iron in donors. That particular session didn't attempt to determine

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

whether hemoglobin is the correct screening test for assuring donor health, or for reflecting iron stores. In fact, it appears not be for the latter.

It was assumed that accurate hemoglobin determination plays some role in preserving donor health, and ensuring acceptable quality of the red cell unit collected. As we heard, there's no product specification for red cells, hemoglobin in the United States.

The focus was on the methods of determining hemoglobin, including donor physiology and the measurement techniques. Dr. Goldman pointed out the need to have a screening assay with acceptable sensitivity to deferred donors below any agreed-upon cutoff value, particularly those most likely to be anemic and most importantly, women with less than 11 grams per deciliter hemoglobin.

The accuracy of the test over the entire range is important for donor counseling. Ideally, the method should be

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

rapid, correlate well with diagnostic values that a donor is likely to get from a personal physician, so as not to confuse our donors, be pain-free, and for operational reasons, it should be mobile, simple to use and inexpensive. There's no such screening assay available right now and unlikely to be in the near future.

Whereas the current U.S. paradigm involves a pre-donation finger stick determination performed on a point of care testing device. The desirability of obtaining the more accurate and reproducible venous sample was raised, even if it might involve qualifying the donor by means of a post-donation determination on a laboratory analyzer.

She described the available methods of hemoglobin determination, including the licensed point of care tests and the promising but yet unlicensed, non-invasive technologies.

The latter methods have higher coefficients

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

of variation, which make them somewhat less desirable in advance.

All of the presenters emphasized the variability of methods, that depend upon capillary sampling. The physiology of capillary beds makes this simple source inescapably more variable. The accuracy versus true hemoglobin, that is, .3 grams per deciliter or a 2 to 3 percent difference, wouldn't influence patient care, but it could have a major impact on the deferral of female donors close to the eligibility cutoff.

Ms. Bautista described the regulatory process for clearance of a screening device, and described the currently cleared devices. Depending on the technology, the level of complexity and the intended use, this may involve pre-market notification under the 510(k) approval process, with appropriate analytical studies and clinical correlation studies, or much more extensive evaluation for technology or uses that have not been based on

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

a predicate device.

Dr. Cable presented data from the REDS studies of U.S. volunteer blood donors, which were gratifyingly compatible with studies previously published by Dr. Murphy's studies of Irish blood donors. Glad to see that. The Irish are no different than the U.S., I suppose in this way.

Both demonstrated that the mean differences between finger stick and venous hemoglobin determinations are different in men and in women, no surprise, and in iron-replete donors. Finger stick determinations, underestimate venous hemoglobin in the upper range, and over-estimate in the lower hemoglobin range.

Dr. Cable further showed, with the REDS II data, that combined gender and iron stores, demonstrating that women with absent iron stores have even a more marked over-estimate by finger stick. However, for men, the finger stick values underestimate venous

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

hemoglobin by .5 to 1 gram per deciliter, and correspond really to the venous value that was recommended by the BPAC, suggesting that perhaps if we stick with the finger stick, there's no reason to change the value.

The study developed regression models for predicting venous hemoglobin, but the model has yet to be verified prospectively. In most iron-depleted women and some iron-depleted men, finger stick hemoglobin overestimates hemoglobin at the donation cutoff level, and leads to the acceptance of many iron-depleted donors with venous hemoglobin of less than 12.5 grams per deciliter.

Dr. Murphy's data did not involve iron depleted donors, but were otherwise essentially identical. He explained the concept of hematocrit variable space, which accounts for the finger stick variability, and presented additional data on the seasonal variation in hemoglobin determinations,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

largely unexplained, but possibly, he speculated, related to temperature or daylight or melatonin effect, possibly mediated by NO inhibition.

A further tantalizing observation was the change in the finger stick to venous gap with age, particularly in females, whose change after the age of menopause approached that of males. The bottom line is that capillary hemoglobin level does not have a simple linear relationship with venous hemoglobin level, and should not be used with venous hemoglobin reference ranges.

Dr. Leitman concluded the session with an evaluation of the usefulness of changes in the red cell indices, particularly mean corpuscular volume, MCV, in managing apheresis donors. Changes in serial MCV determinations accurately predict imminent iron depletion or deficiency, particularly in hemochromatosis blood donors.

Whereas serial determinations of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

MCV, red cell count and RDW, together with venous hemoglobin, determined with an automated cell counter, can reliably predict iron depletion and distinguish iron deficiency from most of the hemoglobinopathies, the methods are really applicable only to fixed sites, and with trained staff. You don't need technologists, however, except where state law requires it. In terms of measurement of iron stores, Dr. Kiss told us that there's no perfect test. He described a variety of biochemical and red cell indices measurements, with an eye to predicting sensitivity and specificity for iron-depleted, or frankly iron deficient blood donors.

Clearly, decreased hemoglobin is a late consequence of iron depletion, and doesn't reflect body iron status. Serum ferritin, the standard biochemical diagnostic measurement for iron stores, is an acute phase reactant protein, but inflammatory disease is fortunately uncommon in blood donors. So this

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

really isn't an issue.

In contrast to the diagnostic cutoff of 12 micrograms per liter, an insensitive measure of iron depletion, levels of 15 micrograms or better, 22 micrograms per liter, it really is sensitive and specific, 90 percent.

Soluble transferrin receptors, also a good test for iron depletion or tissue iron depletion. But there's no uniform reference standard, and it's not currently a clinical test. The log of soluble transferrin receptor to ferritin ratio is being used in a variety of studies of devices in blood donors. FEP is another biochemical measure, and portable devices are available. There are few studies, however, in blood donors.

Overall, for early detection of iron depletion, ferritin of less than 20 is 90 percent sensitive, 90 percent specific for iron depletion, and it's probably the best performer, when compared with other

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

biochemical or red cell indices.

So that was a summary of a lot of data in a very short period of time, and again I would ask if there are any additional comments people want to make or add to that summary of that particular area.

It's the end of the day, and seeing none, why don't we move on, and Dr. Alving is going to talk about iron stores and iron deficiency.

DR. ALVING: I think that Harvey has covered much of this. I think some of the clear aspects of this workshop are the complete separations, essentially, between hemoglobin levels and measures of iron deficiency. It is nice that ferritin, you know, as Harvey said through our speakers today, comes out as the clear winner.

So I think what seems to be an undercurrent here is not a real interest in changing any of the current parameters by which one uses to reject or accept blood

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

donors, and not to change, you know, the interval for donations.

But -- and I think that sounds very acceptable, if one really gets to the crux of the problem, which is the ferritin and the replacement of iron deficiency. If this can be done in a very thoughtful fashion, with real programs implemented, pilot programs to look at how this can be done, along with education. I think that the blood community has an opportunity to provide wonderful beneficial effect, not only for blood donors, for blood recipients, but for our general population.

Now you're going to say wait a minute, that's not our business. But in a sense, it is your business, because you get your donors from all over the world essentially. This is a global activity now, as you look across the world and look at what the other changes are.

I think when we see the successful

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

implementation of iron replacement in Australia, when we see it in Indiana, and we will mention the NIH, although we recognize that is, you know, a special, a wonderful area, that this is going to become more and more of an expectation. When people donate, they expect that they will learn the risks and benefits, and if you were a clinical trial, you would be rejected by the IRB with your current consent form. So I think we have to live up to that.

It will be very interesting to see how the FDA works with NHLBI, works with AABB, works with ABCs and ARC. So you put all of those acronyms together, and do you come out with protocols and maybe not all the centers are involved. But you can sort of divvy it up and decide how you want to do this.

I think there is some skepticism about so what if somebody is iron deficient for a couple of months? Well, I think it depends on where they are in their life cycle.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

I also think it's not a good idea to be iron deficient. So maybe there have been sufficient studies done with iron deficiency and neurocognition.

But as we've said, we've lowered the blood donation age to 16 years of age, without knowing any of the implications in our teenagers. This needs to be studied, not only for neurocognition, but for our young men and women to compete to the max when they're in their tennis tournaments, when they're in their soccer leagues, to know the physiology and to know what it means to start out with totally deplete iron stores on an unplanned pregnancy of which, what 30 or 40 percent are.

So we have to be thinking about our blood donors in a very dynamic fashion, and we are making a big intervention in their lives when we take blood. I think we have to accept that responsibility, and I think they in turn will reciprocate in kind.

DR. KLEIN: Thank you, Barbara.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Are there any other comments? Again, either on Dr. Alving's summary of the iron area, or on any of these summaries, as we close this two-day session?

(No response.)

DR. KLEIN: Seeing none, I think it's been a very educational two days. As I said, there was an enormous amount of new data. Now we'll see whether it will be used to change practice, and whether it will be used to change practice in a way that's reasonable, improves donor safety, improves donor health and maintains the blood system in the United States.

I'd like to call upon Dr. Epstein, if I may, to close the symposium, or Dr. Davey, to close the symposium. Thank you.

DR. DAVEY: We'll get Jay up here, as he's stepping up. I just want to thank the three panel moderators. Those were great summaries, really helped us out. I hope you can provide transcripts of what you said.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

That will be very useful to us.

And then I just want to thank in general our sponsors and the participants in this two-day workshop. I want to especially thank Orieji Illoh, who helped immensely getting this off the ground, as well as Jennifer Scharpf and Mitchell Berger, and all the speakers, for their really great contributions.

Please fill out your evaluations. It's very important for us. I'd like to just ask Jay up here for some concluding remarks.

DR. EPSTEIN: Thank you, Rick. I think also you deserve special thanks for organizing an exceptional workshop. I think we could all agree on that. I also want to extend special thanks to the members of the Steering Committee, who worked hard assembling an outstanding program, and I want to mention them by name. Our non-FDA members included Harvey Klein, Celso Bianco, Simone Glynn, Jed Gorlin, Josh Penrod, Jerry Holmberg and Jim

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

Berger, some of whom were already mentioned within FDA -- Orijei Illoh. Rick himself, Jennifer Scharpf, Mitchell Berger, Les Holness and Teresita Mercado.

I also thank the outstanding speakers and moderators, who made this event possible. My own reflections here are that, you know, we had this FDA-NIH workshop a decade ago. What's happened? Well, the main conclusion from that workshop was the need to step up scientific studies. I think we all should commend the NHLBI for funding and organizing highly significant and highly informative studies, the output of which many of us have heard for the very first time in the last two days.

This is truly a phenomenal contribution. I think it reinforces our sense that there is a problem with iron management in donors, and I feel that there's a general sense coming out of this workshop, that the implication is that we need to do something,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

and the time is now.

I just want to reflect on what I think are the dominant themes. I heard really three things. One is that we have to improve consent to donors, so that we more honestly and completely communicate the risks of donation, and particularly the risks to disturbing iron balance and its possible health consequences. I think the second point that I heard is that we clearly cannot rely on hemoglobin as the basis for managing iron in donors, and that we must now look one way or another at the iron status of the donor.

I would say that a question hangs in the air, to what extent that need exists in source plasma, frequent source plasma donation, because it has not been examined.

I think that two other points are that we need to avoid unintended consequences and therefore proceed with due caution, but that in that context, we already have a very positive experience with management of iron balance and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

also iron supplementation in a number of, if you will, pilot or experiential studies, particularly in Australia and has already been mentioned in several places in the United States.

I think that the large thought coming out of that is that the challenge that we face now is how to operationalize iron management in donors, in the more routine, large-scale setting of the U.S. blood supply.

I think that the challenge was put in front of the FDA, how flexible will we be with pilots, and I would say very simple, science rules. We will always do and always permit that which is scientifically sound, and we have the ability to allow exceptions from regulations, of course under investigation, et cetera, as long as we think that it is, you know, from a scientific point of view, the right thing to do. So I wouldn't leave with any preconceptions that the FDA framework is a barrier. Certainly, we establish our routine

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

practices in our requirements. But they can evolve as we learn more.

So I'm just going to close by reflecting on what were stated as the workshop goals. They were to discuss hemoglobin standards and measurement, and to determine how any change in hemoglobin standards may affect donor safety and the blood supply, to review data on the impact of donation on iron stores, and techniques to assess iron stores in donors.

Lastly, to assess measures to mitigate donor iron loss, such as iron supplementation, I should say replacement Barbara, or change in the interdonation interval, and to evaluate how any such change might affect the blood supply.

My sense is that we've heard a very large amount of very valuable data that we've accomplished our workshop objectives narrowly stated, and we now have, I think, the broader challenge of having heard all this, and having

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

learned all this, do we not have a summons to action, and how do we now proceed?

So you know, with those remarks, I'm going to close the workshop, with thanks also to our very attentive and participatory audience. It's been a pleasure.

(Applause.)

(Whereupon, at 4:07 p.m., the meeting was adjourned.)

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com