BBGuy Essentials 032: Jed Gorlin on Blood Donors and Iron

Joe Chaffin: [00:00:00] You're listening to the Blood Bank Guy Essentials Podcast, Episode 032!

Joe: [00:00:21] Hi everyone! Welcome back to the Blood Bank Guy Essentials Podcast. This is Joe Chaffin. I'm still your host. No one's fired me yet, so I'm going to keep doing this... I'm really happy that you're here today! We've got a15 great topic. We're talking today about blood donors and iron. It's a hot topic in blood bank world, and there's been a lot of discussions on it recently, both at the AABB and FDA level, and really internationally, in terms of the discussion about how to protect donors, in particular the most vulnerable donors, from being potentially damaged by iron deficiency as a result of blood donation.

Joe: [00:00:58] My guest is Dr. Jed Gorlin. Jed is someone I have looked up to for a long time, not just because he's way taller than me, but just because he's a very highly respected and incredibly erudite spokesman for our industry. Jed is a great guy, and I think you'll really like this interview. I also want to thank you for listening to the previous interviews, especially episode 31, the most recent episode, where we talked about the magic of Twitter and how blood bankers should be on Twitter. Please check it out if you haven't had the chance. It's really a fun roundtable discussion with some experts on that platform.

Joe: [00:01:35] So I'm not going to make you wait any longer! Here's my interview on blood donors and iron with Dr. Jed Gorlin.

Joe: [00:01:47] All right everyone, as promised, I am just super-jazzed to welcome to the podcast Dr. Jed Gorlin. Jed, welcome to the podcast, man!

Jed Gorlin: [00:01:55] I am honored to be here.

Joe: [00:01:57] That's very nice of you to say. I want to let everyone know a little bit about you (God knows everyone should know about you already). But the abbreviated version of Dr. Gorlin's very wonderful resume is that Dr. Gorlin is a graduate of Stanford University for his BS and his MD from Yale (you know he's kind of going for the "not so great schools" [laughs]). Jed is board-certified in pediatrics and blood banking/transfusion medicine and he currently serves as Medical Director and Vice President of Quality and Regulatory Affairs of Memorial Blood Centers and Nebraska Community Blood Bank. And both of those are divisions of Innovative Blood Resources. Now Jed has served in just a ton of leadership roles with AABB and other organizations throughout his storied career. And he's spoken and written and published extensively on too many topics to name, both here in the United States and around the whole dang world for crying out loud. I mean honestly, bottom line is that Jed's "the man," and Jed, I think we can both agree that your appearance on this podcast must surely represent the pinnacle of your storied career, wouldn't you say?

Jed: [00:03:10] It is absolutely the *nadir* as you point out.

Joe: [00:03:15] (Laughs) Very nice. Nicely done. Thank you for that. So today you and I are going to explore what to make a bad pun is a very "magnetic" topic and we're talking about iron in blood donors. It's a really hot topic. It's something that a lot of people are

talking about right now. And I want to get to that, but I really always want to start with all my guests with just a real quick figuring out what it was for you that kind of set you on the pathway of blood banking. I know you have a background in pediatrics. What was it...at what point in your career and how did it happen that you got interested in doing blood banking?

Jed: [00:03:58] So in most of the rest of the world, blood bankers are hematologists not pathologists. At Boston Children's, I was a pediatric hematologist-oncologist, and I had an interest in the non-oncological aspect of that, but it's very hard to sort of just do hemophilia or sickle cell, and at least the blood bank was a safe place to hide for a while. I did some training at Puget Sound, came back, and started the pediatric peripheral stem cell program at Boston Children's, and I think that's actually a nice example of how hematology and blood bank can work well together.

Joe: [00:04:43] Nice, and how did you get connected with Minnesota? I mean you've been there for a while. Was that your first place out of Boston?

Jed: [00:04:55] So I moved here in 1997. I do have "ruts" here--not roots, "ruts."

Joe: [00:05:02] Nice! (laughs)

Jed: [00:05:02] I grew up in Minnesota. So for me, it was returning home. For my "Connecticut wife," it was dragging her, kicking and screaming to the flatland.

Joe: [00:05:14] (laughs) Nice. Well, so you've been, as I mentioned, enormously involved with AABB and served in a lot of leadership roles. For someone who's just getting started in blood banking; for a pathology resident, for example, or a resident or a fellow in blood banking, do you have any advice for them on how to get involved in leadership type stuff or be involved in AABB or other organizations?

Jed: [00:05:42] Well, absolutely come to the AABB National Meeting, and there are increasing opportunities to get involved in various committees even as a junior member. But I would also point out, that local blood bank societies are a wonderful way to get involved and are often more than eager to have anybody contribute. In my local case, that would be Minnesota's Association of Blood Banks, but every area has their own local group, and it need not be limited to the blood bank, there's also typically across laboratory organizations.

Joe: [00:06:22] OK. That's a great tip. It is an under-appreciated thing the regional blood bank societies. I'm in California, and the California Blood Bank Society is absolutely looking for people that can help, and I know that you're right. There are regional societies all around the United States and I'm assuming internationally, but I don't know as much internationally. Is that true outside of the U.S. as well?

Jed: [00:06:47] So I have the honor of being the chair of the AABB Global Standards Committee and working with things like the Asia National Transfusion Group, the African Society For Blood Transfusion. Some of the societies are a little more struggling than others, but they are all trying to collaborate in ways that heretofore has not happened.

Joe: [00:07:10] Nice. All right. Well, so I want to get to our topic, Jed, because this is a really important thing and, as I mentioned, it's something that people are talking about A

LOT today, and that's: Iron in blood donors, the iron status and protecting the iron status of blood donors. So we're going to cover five essential facts about blood donors and iron, but before we do that, I guess on background, why are we talking about this now? I mean we've been collecting blood from people for forever, but why all of a sudden does there seem to be this big interest in dealing with donor iron stores?

Jed: [00:07:48] I think it's a constellation of several factors. As health care gets more and more business-like, there's been more and more consolidations and increase efficiency of blood collection. What that means is you go more often to where it's easy to get, and one of the easiest places to get blood is high school blood drives. So we have been dropping the age of eligibility and increasing the frequency and the amount--in the case of double red cells--of blood that we're collecting from younger donors which is economically incredibly efficient, but it may or may not be the right thing to do for their physiology.

Joe: [00:08:37] OK. So is there anything that has brought this more to the forefront? I mean yes, I completely agree that we're collecting more from young donors and that is a potential issue and we'll get to that more in just a minute. Is there any regulatory push for us to consider this?

Jed: [00:08:58] There is. I think the FDA would love for us--the blood collection agencies, to solve this. They really only have two major tools in their pocket. One, is donor hemoglobin level and the other is interval. And so if we can solve it ourselves then that will not force them to make a regulatory change. I have it from a high authority, having had lunch with FDA folks, that if we don't, they will.

Joe: [00:09:35] (Laughs) OK. So the stakes are high. We need to figure this out for sure. So let's start from the beginning with the **first essential fact** about blood donors and iron and that's simply **that men and women are different**. That seems like the most obvious thing to say in the world, that men and women are different, but what do we mean by that? In terms of iron, how are men and women different?

Jed: [00:09:59] So men post-puberty have a higher hemoglobin level than women, but men also have a larger inherent store of iron than women both in muscle and blood. In part, because of the higher hemoglobin there is a higher iron stores. For the typical female, total body iron stores--premenopausal female--are between 300 and 400 mg. One unit of blood that we collect contains about 200 mg of iron, i.e., 1 mg for every mL of packed red cells.

Joe: [00:10:41] Wow. So you're saying that---Holy cow! Let's do that math... and then carry the one...that's A LOT of the percentage of total body iron that we're taking from a woman with a single whole blood donation!

Jed: [00:10:56] Bingo! We take one unit of blood and we have depleted much of the extra stores. We take two units of blood and we're now dipping into the total body iron.

Joe: [00:11:15] Gotcha. So how is that different from guys?

Jed: [00:11:19] Typically, guys will have 400 to 500 mg of iron reserves, meaning they have at least one more unit in their back pocket.

Joe: [00:11:30] Okay, okay. So obviously in blood donor centers we traditionally have not

been--well, let me back off of that. We traditionally have not been, I don't want to say we haven't been worrying about total body stores, but we haven't routinely been measuring it over the years. So over the years we've used, as you mentioned, hemoglobin, to try and determine whether or not a donor is eligible and can you just talk us through a little bit about how those hemoglobin levels got set historically and kind of where we are now with that?

Jed: [00:12:04] So, United States and Canada WERE the only countries that had the same hemoglobin cutoff for men and women and that has changed recently both the United States and Canada. We now have the higher hemoglobin cutoff for men. It historically was that way, and it was somewhere in the 60s or 70s, I forget which, that it was made the same because it was "too confusing" for us blood collection agencies! I am not making that part up! The problem with that is the hemoglobin cutoff of 12.5 actually cuts off the lower one-seventh, about 14% of women. Even with normal iron reserves, the standard distribution curve goes below 12.5 for even people with normal iron. For men, a hemoglobin at 12.5 is almost three standard deviations below the mean.

Joe: [00:13:12] So in other words, we were drawing men to lower levels than we should and deferring women with normal levels.

Jed: [00:13:20] Correct. And if you actually look at ethnic-specific distribution curves, that 14% of women may be actually approaching 30 percent of females of African heritage.

Joe: [00:13:35] Wow. Wow. So you mentioned that other countries--well first, actually before we get to other countries, how has that changed? You mentioned that it's changed recently in the U.S. and Canada. What are the new thresholds?

Jed: [00:13:48] So, the hemoglobin for men was raised to 13, both in the CBS part of Canada and the United States. For women in the Hema-Quebec part of of Canada, they can draw women down to 11.5 if they're of African heritage.

Joe: [00:14:13] So obviously, significantly different. Again take us back to other countries that you mentioned. How does that compare to what's happening around the world?

Jed: [00:14:23] So most other countries are either 12 for women and 13 for men or 12.5 for women and 13.5 for men. And obviously there's hematocrit equivalents which are pretty typically about three times.

Joe: [00:14:39] Okay. In terms of frequency of donation, is that uniform around the world? In other words, how often someone can donate whole blood?

Jed: [00:14:47] Again, the United States and Canada WERE the only countries that had a 56 day or eight-week minimum interval. Almost all other countries have a minimum of 12 weeks. In Canada, they have changed it to a minimum of 12 weeks for women.

Joe: [00:15:07] OK.

Jed: [00:15:08] Or at least are in the process thereof.

Joe: [00:15:11] Gotcha. So I mean, I guess the basic question that I have Jed, is who came up with those numbers? I mean, how did how did we get-- specifically going back to

the hemoglobin numbers--how did we decide that that was a good range for people to donate blood?

Jed: [00:15:31] I think, to be honest, it was more the convenience of blood collection agencies than any given study. In fact, for almost any given blood collection agency the average frequency of donation typically ranges between 1.4 and 2. Meaning you're donating one and a half times a year or two times a year, and very very few people were donating the up to six or more times a year that is allowed with the 56-day interval. So there actually is a wonderful study by Alan Mast of super-donors, people donating six times a year, and he realized that he was thinking that they might have a disproportionate representation of donors with hemochromatosis. In fact, he found a higher frequency of donors who smoke.

Joe: [00:16:36] Oh really! (laughs) That is a different thing, obviously not something we ask about.

Jed: [00:16:42] Nor do I recommend that we give out cigarettes instead of cookies!

Joe: [00:16:46] (laughs) Okay, write that down, "No cigarettes..." OK got it, good! Okay, so I think we've explored that a little bit in terms of the first essential fact that men and women are different. So I want to take that a little farther and let's get to what evidence do we have for **fact number two**, which is, that **blood donation really does impact iron stores**. So Jed, we had a really big important study that came out I believe in 2011, that was called the "RISE Study," if I recall. Can you take us through a little bit of some of the important findings about, to support that fact, that blood donation really does impact donor stores?

Jed: [00:17:31] So there certainly have been a number of excellent studies around the world including Canada, United Kingdom, Ireland, and Australia. But the RISE Study was a very nice, well-organized study looking at donor frequency and iron stores. And one of the contributions it made was using not just ferritin but some additional fancier studies of iron, which allowed sort of distinction between "absent iron stores" [NOTE: AIS] and "iron deficient erythropoiesis" [NOTE: IDE]. Sort of two levels of deficiency with absent iron stores being completely absent and iron deficient erythropoiesis meaning---you're getting there. And what it showed is, men or women, if you are female and donating two times a year or more, if you are male and donating three times a year or more, there is a very high likelihood of at least being low in iron stores, either the absent or iron deficient erythropoiesis.

Joe: [00:18:45] So take it back to the beginning, just again, since we have a very wide range of people in terms of expertise that are listening to the podcast. Just if you don't mind, talk to us for just a second about about ferritin measurements and what they mean. What does a ferritin measurement tell you about a donor?

Jed: [00:19:04] So free iron is a really bad thing. Free iron can cause you to rust. It is an active oxidant, and so, our body actually does a wonderful job from protecting us from rusting. So it has various molecules to hold on to iron to make it readily available to use, but not to allow it to be wreaking havoc on various tissues. And so one of the storage proteins is transferrin. Another storage protein that actually holds a larger amount is ferritin. So typically, if the ferritin level gets below 20 or 30 it's sort of a low level and if it's below 10 or 12, it's a very low level. There are fancier measures, transferrin receptor was

used in the RISE Study, and it's perhaps a slightly more sensitive and quantitative receptor than ferritin. The problem with ferritin is it is also an acute phase reactant, so other forms of infection or inflammation can cause an elevated ferritin level, which does not mean that you actually have extra iron.

Joe: [00:20:30] Okay, okay. And you mentioned the two categories that the testing put these donors into the RISE Study: The absent iron stores and the iron deficient erythropoiesis. I think absent iron stores is pretty self-explanatory, but can you quickly help us understand what iron deficient erythropoiesis means, IDE?

Jed: [00:20:51] So, this sort of reflects the MCH or minimum corpuscular hemoglobin concentration. So if you have cells that have less than the typical amount of hemoglobin in them, that would be a sign that you're trying to make hemoglobin, you just don't have enough stuff to fill up the bag.

Joe: [00:21:19] Gotcha. Okay. So maybe a step on the way to absent iron stores but just not quite as severe a deficiency.

Jed: [00:21:27] And we see this as hematologists as pale red cells.

Joe: [00:21:32] Got it. Got it. Okay. So you mentioned that there was a significant amount of both iron deficient erythropoiesis (I can't even say it), and absent iron stores in frequent donors. Was there a difference between males and females in that data?

Jed: [00:21:53] So, yes and no. If you look at first time donors, i.e., people we have not collected any blood from, very few males are deficient in iron. If you look at first time females, it is somewhat age and menstruation dependent. So, first time females who are younger, i.e., pre-menopausal, can have a 10 to 20 percent rate of iron deficient erythropoiesis. And if you look at high school females, so those easy-to-do blood drives, that can be 20 to 40 percent. So we're starting off with a group who has a higher risk of already being low in iron stores. For males, that's essentially less than 2 percent.

Joe: [00:22:49] Got it. Got it. And is it correct to assume that, so you mentioned that for first time donors, for more extensive donations, do those numbers kind of extrapolate? In other words, is iron deficiency seen less in male frequent donors than female frequent donors or does it equilibrate?

Jed: [00:23:11] So "we have met the enemy and they is us." When you get to really frequent donors, three, four, or five times a year, 95 percent of them will either have absent iron stores or iron deficient erythropoiesis. So if you take enough blood, everybody is iron deficient.

Joe: [00:23:29] Wow. "We have met the enemy and they is us," I know that phrase! What's the origin of that, Jed?

Jed: [00:23:37] That was from a "Pogo" cartoon I believe actually during the Vietnam war.

Joe: [00:23:45] That's awesome! So anyone younger than us is going to go, "Pogo, I've no idea what they're talking about," but that's ok.

Jed: [00:23:52] I'm showing my gray hairs.

Joe: [00:23:55] So I think that that RISE (as well as other data that's out there, and we'll talk a little bit more about that in just a second) pretty clearly answered the question for fact number two, which is that blood donation really does impact donor iron stores. I don't think there's any question about that. But let's move on now to fact number three which I think is really, really important for people to understand, because I hear this a lot from donors in particular, and especially when the male threshold in the United States went up from 12.5 to 13 g/dL of hemoglobin. They said, "Well I don't understand why this is a big deal! My hemoglobin...I always qualified before." So **fact number three** is that **hemoglobin is actually a poor predictor of donor iron stores**. So Jed, how do you answer that question when your donors say that? Why can't we just say, "Hey, you know what, you're good! You met the threshold!?"

Jed: [00:24:51] So it is true that if you were really, really iron deficient, i.e., absent iron stores that you are at much greater risk of anemia, i.e. a low hemoglobin level. So while it is true that people that are grossly iron anemic have a higher probability of not passing the minimum hemoglobin, especially for men, where the cutoff was three standard deviations below the mean, there were plenty of men still making the cutoff that were iron deficient and recognizing that that 95 percent of the really frequent donors are iron deficient at least in their iron stores, one can see that we're drawing a lot of people that, you know, don't have a whole lot of reserve.

Joe: [00:25:51] Yeah, yeah. And I think that one fact is something that---speaking for myself at my blood center in Southern California, I think donors have the hardest time understanding that and just getting that message across has been a challenge and we're trying to do that in language as simple as possible. Are you having those discussions as well, Jed?

Jed: [00:26:16] Joe, it's not just the donors! It's our own staff!

Joe: [00:26:19] You're right about that! (laughs)

Jed: [00:26:21] "Oh, your iron is good today!"

Joe: [00:26:25] (Laughs) Okay! Pet peeve time! When the staff is telling the donors we're going to "check your iron," is it just me or does that make anybody else crazy?

Jed: [00:26:36] I'm afraid it helps confuse the donor and gives the donor the idea that we are truly protecting their iron stores which we have no way of doing, in the absence of measuring the ferritin.

Joe: [00:26:49] Gotcha. Very very important. So I don't want to spend a whole lot of time on fact three, Jed, because we've got a lot to talk about with the next fact, but let's just see where we've gone so far. We've said that fact one, that men and women are different. We've explored some of the history of the thresholds and everything. We've talked about fact two, which is that blood donation really does impact iron stores, and in particular, discussed the RISE Study. And by the way just as an aside everyone, the references for the papers that we're talking about in this podcast today, will be on the Blood Bank Guy website, on the show page: BBGuy.org/032. You'll get all these references so you can look them up yourself. Fact three was that hemoglobin is a poor predictor of iron stores. Now we get to the big one that we really need to dive into a little bit, which is **blood collectors**

REALLY need to do something about this. So, before we get to the specifics of what AABB and FDA rumblings are, Jed, I think it's important for us to ask this question: So now we have data that shows that blood donors have at least some degree of iron deficiency that correlates with the more times they donate that they have some degree of it, but this is NOT NEW. We've had people donating blood forever. Do we have evidence, conclusive evidence that this is actually hurting people?

Jed: [00:28:17] So that's a little harder. Most people that are somewhat to moderately iron deficient don't have such severe symptoms that it's causing them immediate problems. Certainly people, some people manifest iron deficiency or low iron stores with some rather interesting symptoms including "pica," a sub-type of which is called "pagophasia" or the tendency to chew on ice. It's probably our body's way of trying to find iron from other sources. There are studies certainly in other settings than blood donors that clearly show other significant impact of iron deficiency, i.e., wearing my hat as a pediatrician, there are multiple studies showing that iron deficiency impairs learning.

Joe: [00:29:19] Yikes. And especially when you're talking about the younger generation that we're collecting more, perhaps than we used to, that does seem to---that's alarming.

Jed: [00:29:30] Iron deficiency also can decrease energy and exercise capacity, which certainly would affect not only our student athletes, but all of those that are actually expected to do stuff.

Joe: [00:29:44] Yeah. Okay. So, back in 2012, Jed, as you are very well aware, AABB put out Association Bulletin 12-03 and that followed some discussion that had occurred in November of 2011 at an FDA workshop. I wonder if you could talk to us about both of those? I guess, starting chronologically, with the FDA workshop in November of 2011. What kind of came out of that?

Jed: [00:30:17] So it was really a wonderful "bringing together" of the literature that was already there, and it did document that hemoglobin was a poor predictor of iron status, that there were studies showing that what we typically do to measure hemoglobin, i.e., the finger stick, is a pretty good measure of venous hemoglobin but far from perfect. And that we should have some allowance that the finger stick could be up to half a gram or even a gram off, which was the reason that the earlobe sticks were discontinued, because they were actually at even much higher standard deviation of inaccuracy. And, that there were pilot studies showing that ferritin was a reasonable surrogate measure of iron stores.

Joe: [00:31:23] So, now that did not, as I recall, lead to any---it was more discussion than it was any regulation coming out of that, correct?

Jed: [00:31:34] Correct. That was really the beginning of the FDA saying, "Hey you guys do something about it." And so the AABB created an inter- organizational committee, which included our Canadian colleagues. But basically the charges there were to develop a donor information sheet which was done. Develop recommendations in the form of the Association Bulletin, and then monitor some of the mitigation approaches that various blood collection organizations were doing, so we wouldn't be reinventing the wheel. So we could immediately learn from each other.

Joe: [00:32:11] Got it. So that came out in 2012, that Association Bulletin 12-03, as you mentioned before. So I want your honest opinion as best you can give me Jed: Would you

describe the United States blood industry response to that as "overwhelming," in terms of the activity that it stimulated?

Jed: [00:32:41] So credit where credit is due, it certainly stimulated additional NIH-funded studies. And I think, it's important to really have parallel actions. One, blood centers doing something, but also to study the various options in a more rigorous fashion because the minute you do something as an entire organization, it becomes very hard to tell whether that was a good idea or not. Bad ideas are pretty obvious, but it becomes very difficult to actually measure given that typically blood centers may be doing lots of different things at the same time. And so, you know, whether or not it's necessary or helpful to measure ferritin? If everybody's iron deficient, do you really need to measure ferritin? Well, I mean a lot of those studies were done in frequent blood donors, and so, there still may be a role for measuring ferritin. Some centers did. Mayo went to a minimum of 12 weeks and showed that their deferral rate upon return, dropped significantly.

Joe: [00:33:56] Okay. So I didn't mean to be facetious there. Speaking from someone, from the perspective that I have, from someone who is Medical Director of a local blood center, I think that it was difficult to know exactly what pathway to embark down when that bulletin came out. And so, I don't mean to be unfair to my colleagues, but I think that a lot of places took a, "Let's wait and see," type of attitude. And as you pointed out, I don't know that that's incredibly unreasonable. But further, in the interim, as time went by, some studies actually did come out. And Jed, I wanted to call everyone's attention to a commentary that you wrote in March 2014, I think it was a supplemental edition of "Transfusion" regarding blood donors. And your article, your commentary was entitled, "Ironman Pentathlon (I love that!) Or, We have met the enemy and they is us," your phrase that I love. I don't want to spend a ton of time on that because I want to get to the kind of landmark studies. But you summarized five studies that were published in that particular edition of Transfusion. Can you kind of just give us an idea of what those studies contributed?

Jed: [00:35:17] So, I mean I think they were all excellent single center studies showing that more frequent blood donors were more likely to be deficient in iron, that replacing iron did decrease magnitude of iron deficiency. But one that I thought was particularly intriguing, was that dietary iron recommendations, while well-intended, were simply ineffective. And so, every blood collection agency I know has well-intentioned, "Donors should eat iron-rich diet and you know eat your spinach and be like Popeye!" The practical reality is very few people eat enough dietary iron that they can truly replace very frequent blood donation. So while dietary recommendations are well intended by themselves, they are completely insufficient to replace iron if you're going to be donating three, four, five, six times a year.

Joe: [00:36:29] And I agree with you. That's such a huge thing because we have relied on that advice for our donors for so long, and that particular study which I believe is the Danish Study, is that correct? Yes...that one will be referenced on the show page as well everyone. That's a really important study as well as Jed's commentary. So those added some additional information that kind of helped us understand some things and again, the dietary iron was a big deal. But there are three big studies; two in particular that have been published and one that I think is on the way to being published, that blood bankers need to know about, quite frankly. They are the HEIRS Study, the STRIDE Study, and finally, the CHILL study, that's the one that to my knowledge has not been finally published, but we know some information about it. So Jed, can you take us through those? Can you take us,

starting with the, I think in chronological order with the HEIRS Study?

Jed: [00:37:28] Yeah. So this was actually a fascinating study showing that hemoglobin recovery was much faster and better if you took iron. And while it shouldn't be rocket science that if you give iron to an iron-deficient person that they recover faster that's in fact exactly what it showed. So it took again very frequent donors, so women donating two or more times a year, men donating three or more times a year. So you've already...it's a subgroup of your regular donors, divided them up into people that were starting with a low ferritin (and they define that as less than 26 ng/mL) or a higher ferritin (higher than that), and then looked at how long it took them to recover their hemoglobin level back to baseline. And in a nutshell if you were not on iron and you had a reasonably high baseline level of ferritin it took you typically 90 to 120 days to recover your hemoglobin, which is longer than the 56 day interval. In fact, the rate of deferral for low hemoglobin does not come back to normal until 26 weeks, showing that for most people with just standard dietary iron it takes half a year to completely recover your baseline hemoglobin level and that's not iron stores. If you replaced the iron, and they were getting the equivalent of about 38 mg elemental iron for at least an eight week period, almost everybody recovered their hemoglobin level to at least 80% of what it was, or at least 80% of the deficit within that 56 day period.

Joe: [00:39:48] And they were measuring ferritin, so we have an idea of how fast the ferritin came back up too, right?

Jed: [00:39:54] Correct. And so, if you got the iron replacement, most people were up to baseline by about 80 to 90 days. And often even higher if you kept taking the iron. If you did not have iron supplements, typically it was half a year or more. And actually many people were not even at a half a year completely back up to their original ferritin level.

Joe: [00:40:30] Super-important information! Jed, I know that there was...the study came out in JAMA in 2015, but I know there was a secondary analysis that came out in Transfusion in 2016 that talked about kind of the the peak time to supplement in terms of the iron effect and where the iron effect has the most impact. Can you talk about that, what they found there?

Jed: [00:40:55] So this was Ritch Cable's study that basically showed taking iron in the first eight weeks after the donation had the highest impact, had the highest yield. Beyond 8 weeks, while your iron, your ferritin continued to go up, the slope of the curve was identical to standard dietary iron at beyond eight weeks. That doesn't mean that taking additional oral iron isn't helpful beyond eight weeks, but clearly the place where it made the big difference was in under eight weeks, and hence the recommendation of most centers that if you're going to take iron at least take it for eight weeks.

Jed: [00:41:45] Got it. OK. So HEIRS was incredibly important and STRIDE, the next study we'll talk about, the "STrategies to Reduce Iron DEficiency," which was published I believe in Transfusion in June 2016. There were several parts to the publication I think, but the main results were published then. So can you take us through that? What did STRIDE find?

Jed: [00:42:06] So this was an absolutely fascinating study! Five arms to the study. One arm was a donor letter. So everybody had their ferritin measured. And again this selected from frequent donors, men three more times a year, females two or more times a year, but

then divided them up into five groups. Two of the groups got a letter one of which said, "Hey, your ferritin is low! You should do something about this. Here's your level, and you know we recommend you take iron and show your doctor, and blah blah blah." The other said, "Thank you so much for donating! You've saved lives, and you are a hero!" and other totally sweet but irrelevant stuff. The treatment arms included a placebo, and then iron replacement, but fascinatingly, iron placement at a quite low versus a moderate level. What I mean is if you go in to the drugstore and ask for iron they will typically give you ferrous sulfate, which at 325 milligrams has about 60 to 70 mg of elemental iron. And the reason a lot of people don't like to take iron is it tends to give GI upset, cramps, dark poop, and other stuff people don't like. The form of iron they gave had about 38 mg of elemental iron, which is sort of a moderate dose. But the other dose was a low dose of 19 mg, half that. And if you go into the Costco and get multivitamins with iron that's the sort of, 18 or 19 mg is the standard dose of iron in multi-vitamins with iron. And that's sort of a daily dose, as opposed to the replacement dose that we're sort of used to giving people that have, you know, frank iron deficiency anemia. And the fascinating thing was it didn't matter in this study whether it was the 19 mg or the 38 mg of iron, that was equally effective, and most amazingly, what was equally effective was the donor iron letter, which said, "Oh, by the way you have low ferritin!" What was not effective was the control letter, or not surprisingly, the placebo.

Joe: [00:44:50] Yeah that's certainly true. One question Jed (and they say never to ask a question you don't know the answer to, but I'm going to do it anyway), the group that got the letter suggesting they either lengthen their interval or take iron: Do they know what proportion of them took iron?

Jed: [00:45:09] There is some but incomplete information on that. A significant proportion took iron.

Joe: [00:45:18] OK, all right. So I mean, that's huge. So there's a lot of things that came out of STRIDE but what you just said about being able to take a really low dose of iron and have it be just as effective as a moderate dose, theoretically at least without the significant side effects. Is that the case, that you avoid some of the side effects with a lower dose?

Jed: [00:45:40] Well maybe! What is clear is you have a significant number of side effects with placebo.

Joe: [00:45:48] (Laughs) Ah, gotcha.

Jed: [00:45:49] So interestingly, all three treatment groups had significant side effects. There was a higher drop-out of this study of people that got the iron. So clearly, if your poop turns black, some people don't like that, and will stop taking it. I would have a slight caution on over-generalizing....the results are the results, and that's what they found. In Canada, they did a very large-scale study of sending letters that "You have low iron." And it did have a significant effect: The donors stopped coming back. So, while it certainly helped the donors, it didn't help Canadian Blood Services. The second thing is there are other studies especially in the maternity literature showing that a higher dose of iron is better on preventing or mitigating iron deficiency. And the 19 mg dose is not as as effective as the 38 mg dose, and replacing iron in people that are clearly iron deficient. And then finally, understand that people that sign up you know for these studies, one, they were selected from really frequent donors so they're already motivated. They signed up for this study, and then they came to the completion of the study. They stayed with it all the way

through, so you now have a reasonably select group of highly motivated donors which may explain why this study found that a letter was just as effective but the letter in the much larger scale Canadian (Mindy Goldman's) study showed that mostly they came back less.

Joe: [00:47:46] Gotcha. OK. OK that's that's fair so. So good and encouraging results, I would think, but your grain of grains of salt are noted. Understand. So the last study which is again unless I'm wrong which I feel like I am all the time I don't believe has been finally published is the study the "Comparison of the History of donation and Iron LeveLs in teen blood donors" that I believe was discussed at the FDA Blood Products Advisory Committee back in November of 2016. Can you again, since it hasn't been published I guess we can summarize what's been said, but can you just take us quickly through that?

Jed: [00:48:26] So I was at the FDA BPAC meeting so I did hear some of the results but I make no claim to having a particularly absorptive mind. I think that the major take-home lesson was that teenagers are disproportionately high at high risk for low iron stores and that even moderate frequency donation resulted in depletion of those iron stores. And so blood centers that pride themselves on four or five or six times a year blood drives at high schools are probably putting a more vulnerable group at higher risk.

Joe: [00:49:15] It is sobering for sure especially given what we've discussed at the beginning about how we're collecting more and more from from the young kids. OK, so again let's get us caught back up. We've talked about the five essential facts: Number one, men and women are different. Number two, blood donation really does impact donor iron stores. Number three, hemoglobin is a poor predictor of donor iron stores, and we just covered the fact that blood collectors need to do something about this and some of the studies that have discussed how to do some of those things. So that brings us to the **last fact** which is (and there's a little bit of editorial opinion in here, I'll admit, so maybe fact is too strong a word) but I think from the studies, I think that it's safe to say that **giving iron and testing for ferritin are potential good options**. And Jed, I know you have something personal about this, that you can discuss a study that that you that your center did. Can you just take us through that?

Jed: [00:50:18] Yeah. So in fairness, this study started around the same time as the RISE study was completed, sometime around the HEIRS study. So it preceded the STRIDE study.

Joe: [00:50:33] Gotcha.

Jed: [00:50:34] So it's not exactly earthshaking, but it was really more of a practical effectiveness study. One of the objections we were hearing at the 11/12 FDA summit and the time the first AABB bulletin was produced was, "Oh, blood centers can't be dispensing iron. We're not, you know we're not taking medical responsibility for the donors." And so Louie Katz at Davenport and I just wanted to do, can we measure ferritin, and can we dispense iron? And the answer is: Well of course! Now, in fairness, we did these studies at fixed sites, and typically our main fixed site, and one of the outcomes was the cost to mail the iron to donors found to be iron deficient on a ferritin assay was three times the cost of the iron itself. And so, while we showed you can do it, it doesn't mean it was terribly logistically practical.

Jed: [00:51:46] So there were two main issues. One, ferritin is not a typically available or

convenient point of care assay. It's best done as a batched assay. So what we were doing was taking a sample of the unit when collected, or in the case of women with hemoglobin of 12 to 12.4 a venous blood sample, and then doing that as a batch test once every week or two and then sending out those results with the iron. So Dr. Katz tried a point of care test, zinc protoporphyrin. If you don't have iron to put into the heme ring, then you will have its precursor zinc protoporphyrin flying free. So if you have an elevated zinc protoporphyrin level, you are likely to be iron deficient. And while that is technically true, it's not a test with a sufficiently robust positive predictive value, or negative predictive value for that matter. And it's also a terribly expensive point of care test. So while it makes great science, it's not a terribly practical test to use for blood centers so I think one thing that came out of this study, though wasn't in the original published report was that zinc protoporphyrin is not a terribly practical alternative for a point-of-care test. The other was, when we put people on iron, when they came back their deferral rate was dramatically lower. So we had something like a 23% deferral rate if they didn't get the iron and a 5% deferral rate if they did get the iron. So it's actually in blood centers' self-interest to ensure that our donors have iron adequate iron stores.

Joe: [00:53:47] And I think what you just said about about how it can help you on the other end, as well as doing good for the donors and the fact that it's feasible to do this, feasible, but as you said not necessarily the easiest thing to do. Those were really important things that that you guys showed. And that really kind of takes us with bringing everything back into context all the stuff that's been published, all the stuff that's been looked at. The AABB tried to kind of synthesize all that in a fairly recent Association Bulletin AABB Association Bulletin 17-02, which kind of circled back around to the bulletin from 2012 and expanded and updated it. And I wonder if you if you wouldn't mind taking us through that, the basic ideas in that bulletin?

Jed: [00:54:41] So I mean it's you know it's hard very similar to the 12-02 bulletin, but I think trying to push it one step further. It's basically saying, "Stepping back and saying waiting for studies is no longer adequate," and that all blood collection agencies should implement one or more intervention and whether those interventions are directed at all donors or specific subgroups is really up to the blood collection agency. Recommended specific subgroups to pay attention to be young donors ala the CHILL study, pre-menopausal women, or those who donate frequently (two more times a year for women or three more times a year for men). Whether iron supplementation is best done by handing out the iron, giving vouchers, recommending iron alone versus multi-vitamins plus iron, I think would benefit from further study and the guidance is very nonspecific about that. And then finally, either lengthening the interval or limiting the number of donations per year. I'm actually more attracted by the limiting number of donations per year because that would still allow you to you know make up during a shortage period between Christmas and New Years. But saying you know, maybe donors shouldn't donate more than four times a year. It's really the total number of donations over the previous year or two that has a greater correlation with iron stores and specific intervals. And again measuring ferritin or other measure of iron stores, you know that that certainly would help guide interventions, but with really frequent donors having a very high rate of low ferritin may or may not be actually necessary.

Joe: [00:56:52] And so let's hone in for just a second on the lengthening interval versus limit donations thing because I think that's an interesting thing to discuss. I think we're good with iron supplementation and I think the things that we've discussed are ready about about measuring ferritin and all that, I think we understand that those work. But I think that

when blood centers see things about lengthening the interval or limiting the number of donations, we have a tendency to kind of tighten up and go "Oh my goodness," because most of us are aware that blood donations in general are down (thank goodness, transfusions are down), but donations in general are down across the United States and I think it's kind of international as well. And if we're going to lengthen the interval you know based on some of the stuff you said earlier without without iron we may be talking like six month intervals. So how do you respond to that one when blood centers get really nervous about that idea?

Jed: [00:57:46] So I will point out that almost every other country does fine with a minimum interval of 12 weeks. I don't know that anybody is suggesting limiting intervals to a half year which would be the natural recovery time. But certainly there are countries where they limit females, i.e., groups at higher risk to three or four times a year. I will also point out that blood establishment computer systems are currently designed to make it very easy to adjust the interval to whatever we want. They're not at all designed to count the number of donations in a rolling period which would be it would be a bigger flog change.

Joe: [00:58:47] Mm hmm. Okay. So Jed the last thing that I just want to I want to mention is that I'm sure that there are some people out there listening to this podcast saying, "OK so you're talking about whole blood donation. How does any of this apply to apheresis donation?" So can we close with that just quickly, any any thoughts on that, about apheresis donation and this whole issue?

Jed: [00:59:11] So you don't lose a lot of red cells with an apheresis donation, but you do lose some. So one there is 20, 30, 40 mLs left in the circuit depending upon the particular apheresis device. But more importantly, that diversion pouch which we use for doing the infectious disease testing, contains 30 to 60 mLs of blood. And this is you know not terribly relevant if you're like me and donate platelets once every one to two months. If you're going for the 60 gallon donor board and you're donating 24 times a year doubles. That absolutely adds up. And so, New York Blood Center and others have done this study looking at iron deficiency and frequent platelet donors, and the answer is yes. Interestingly, in the plasma collection industry the FDA allows them to do the infectious disease testing from the collected product plasma as opposed to the diversion pouch which means they're not losing that extra volume of red cells with each donation.

Joe: [01:00:31] Interesting. I wasn't aware of that. That is interesting. And of course if we're talking about someone who's donating red cells by apheresis, then I mean the rules are essentially the same unless it's a double red cell and there are additional considerations. But when I say apheresis, obviously I'm referring mostly to platelet donations by apheresis.

Jed: [01:00:50] Well, I would point out that an unnamed organization had a publication that double red cells have a lower adverse reaction rate because you're not changing the donor volume and are therefore especially preferable in high school donations. And as the reviewer of that article, I objected strongly saying yes, but that's the exact group that's of greatest risk in iron deficiency. And one should have caution. While double red cells again may be more convenient in that population that may be exactly the wrong population in which to be doing lots of double red cell collections.

Joe: [01:01:35] I hear what you're saying. So Jed this has been great! I really can't thank

you enough for doing this. Everyone just to remind you we've we've talked about five essential facts of blood donors and iron, we've done **men and women are different**, **blood donation really does impact donor iron stores**, **hemoglobin is a poor predictor of those donor iron stores**, **blood collectors need to do something about this**, and all the studies that talk about how to do it, and then finally **giving iron and testing for ferritin are potential good options**.

Joe: [01:02:04] Jed, seriously, it's been an incredible honor to have you here. I'm wondering, do you have any last thoughts on anything we've talked about or anything else before we close?

Jed: [01:02:15] At the risk of being a little political, I would like to point out that the RISE, HEIRS, and CHILL studies were all wonderfully funded by collaboration with the NIH on the NHLBI funding grants, and if current budget or proposed budget were to go through, the NIH would have significant cuts that would certainly prohibit any additional of this sort of study. So I would urge everyone to be advocates for the kind of NIH funding we want, so that we can continue to do these sort of important donor health studies.

Joe: [01:02:55] They are important and it's good work that's being done. So Jed, as I said, it has been my honor. Thank you so much for being my guest today!

Jed: [01:03:04] Thank you so much, Joe.

Joe: [01:03:09] Hi, this is Joe back with a couple of closing thoughts. You know, Jed and I have been working on getting this podcast going for some time, and coincidentally, right around the time that we did this recording, there were a couple of things that came out from AABB that I think are very important to call your attention to. The first was an AABB eCast on May 15 that Drs. Joe Kiss and Ralph Vassallo presented, and it was really a terrific job that they did summarizing a lot of the same topics that we discussed today. There is a lot of overlap between what Dr. Gorlin and I said today and what they said. I would highly recommend that you get a copy of that discussion and listen to that as well. In addition, AABB announced the formation of an ad-hoc committee to look at iron management among blood donors. That came out during that same week, actually, the same week that we recorded this podcast, as well. So, again, there is a lot of activity going on on this topic, it is, as I mentioned, a "hot topic," and a lot of things are happening with it. I've included a lot of references on the site, as well as a bunch of slides that Jed has put out. That is BBGuy.org/032.

So, my thanks to Dr. Gorlin and thanks to you for listening!. I hope that you'll go to that show page and check out what we have there. In addition, if you go to BBGuy.org/subscribe you can sign up to be notified of any new content such as this and stay up to date. That would be great. And if you get the chance, at some point when you're on your computer, just run over to iTunes and give this podcast, the Blood Bank Guy Essentials Podcast a rating, and if you want subscribe, again so you'll automatically get the podcasts when they come out brand new.

So again, thanks to all of you. I hope you have a wonderful day and as you go through that day, I hope that you smile, I hope that you have fun, and above all, hey, please never ever stop learning! Take care. We'll catch you next time on the podcast.