BBGuy Essentials 045:
Past, Present, & Future with Harvey Klein

Joe Chaffin: This is the Blood Bank Guy Essentials Podcast, episode 045!

[INTRO MUSIC]

Joe: Welcome, everyone! My name is Joe Chaffin. I'm really glad that you're here today!

I just want to let you know right up front that this is *not* a continuing education episode. You can check BBGuy.org and TransfusionNews.com to look for episodes ending in "CE," and those are the episodes that are continuing education for you to get credit. Those CE episodes are provided by Transfusion News with generous sponsorship from Bio-Rad (who, by the way, have no editorial input into the content).

I almost can't *believe* that I get to introduce today's podcast guest! When you think about people who have truly made an impact in transfusion medicine, people who have been at the forefront of new and exciting frontiers in our field, there aren't many who are more deserving of the title of "giant" than Dr. Harvey Klein. Dr. Klein is Chief of the Department of Transfusion Medicine at the National Institutes of Health in Bethesda, MD, and has been since 1984. Among his honors, which are really too numerous to count, well, let's see: He's a former AABB President, he's co-author of the 12th edition of a great book, "Mollison's Blood Transfusion in Clinical Medicine," and he most recently, at the 2017 AABB Annual Meeting, he was awarded I believe AABB's highest award, the Bernard Fantus Lifetime Achievement Award.

I contacted Harvey initially because I wanted to talk about an article that he and and a couple of co-authors had written in the *New England Journal of Medicine* about the current and future state of transfusion medicine, and we are going to discuss that in the interview you are about to hear, but I quickly realized that Harvey just has so many things to say, and he's been heavily involved in so many amazing things since he got to the NIH in 1973, and I just wanted to hear all about them, too! So, today's interview is really about the "Past, Present, and Future" through the eyes of a giant of transfusion medicine! So, now, I get to say 7 words I thought I would NEVER get to say, and here they are (you ready?): "Here's my interview with Dr. Harvey Klein!"

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Joe: [00:02:23] Hi, Harvey! Welcome to the Blood Bank Guy Essentials Podcast!

Harvey Klein: Thank you. It's great to be here.

Joe: You know, when I first started this podcast in 2016, there were a few people that were on my list of, "Boy, that'll never happen, but I'd love to get THAT person on the podcast!," and I have to admit, Harvey, you are right at the top of that list! So, I'm unbelievably honored that you would spend this time with me.

Harvey: Thank you. Flattery will get you everywhere.

Joe: I like it, I like it! (laughs) So many people that listen to this podcast are just kind of getting started in the field, and may not know a whole lot about transfusion medicine, and you are someone who, as I said, has such an incredible background. I wonder if you would just give us the thumbnail on what got you started in transfusion medicine, and what got you interested, and what kind of keeps you going in it today?

Harvey: Sure. Well, I was a newly minted hematologist in 1973 when the Vietnam War was hot and heavy, and I came to the National Institutes of Health as my obligate service. And as a hematologist, I came to the newly founded blood division of the Heart, Lung, and Blood Institute. I had the good fortune of being in the division with Dr. Ernie Simon who had just arrived at the same time. Dr. Simon was also a hematologist, but his work had been done in storage of red cells in the University of Washington in Seattle. He convinced me that one of the areas in hematology of real opportunity was in blood transfusion, especially for someone who was a clinician, because most of the transfusionists at the time were pathologists, and were much more laboratory-oriented than patient-oriented, and that's how I got into the area.

Well I came here for two years just for the obligate service and actually still had a position at Johns Hopkins, where I trained, waiting for me, but it was such a great place to be! I met the people in the hospital, Dr. Harvey Alter, Dr. Paul Holland, who were doing blood transfusion. The idea of being at a place where you could do translational research, and that was THE product, was just so attractive to me, that I came for two years and that was 43 years ago.

Joe: (laughs) Well, I think you might be fairly well established there then.

Harvey: Well, I'm probably a lifer.

Joe: That makes total sense! Well in that time, Harvey, you have not only seen, but you've been kind of at the epicenter of a whole bunch of what I would describe as paradigm shifts, sea changes; just BIG things that have happened in our field. And I

wanted to talk to you about just a few of them, some of which are obviously big, huge, and widely known, and at least one of which is one that I think is a great bit of trivia, and I'll get to that in just a second. But I want to start with the very first one that's, wow, I think everyone would agree has completely changed what we do in transfusion medicine over the years, and that is the discovery of HIV, and HIV being transmitted through blood transfusion. And again, I know you and the NIH were very much involved in that whole process. I wonder if you would tell us the story a little bit about your involvement and your perspective on that?

Harvey: [00:05:56] Sure, and that was another great thing about being at the NIH. Whereas, the extramural people have to apply for grants, the people who were here at NIH have a research budget, and it's fairly flexible in that we are reviewed after we've done our research, every four years. So we're very flexible, and when HIV, before it was KNOWN as "HIV," appeared on the horizon as a rare disease, we actually were able to import people to the Clinical Center of the hospital here at NIH and begin looking at this very unusual disease. I was fortunate in that I had a young collaborator here for other areas by the name of Anthony Fauci, who has gone on to other things, as most people know, but was one of the real movers for HIV. He was the one who imported these patients from Chicago, and Los Angeles, and San Francisco, a rare disease.

Joe: It's a little bit hard for people that are obviously newer in the field to understand the import of all that happened back then. How did you become aware that something was going on in the blood supply?

Harvey: Well, there were a couple of papers that were published that suggested that this immune deficiency could be acquired and could be acquired by people who had been exposed to blood components. For example, patients with hemophilia, and children, and there's certainly one in Los Angeles who received a platelet transfusion as a neonate, and developed an immunodeficiency syndrome. And so, we had been very interested, as you know, in post-transfusion hepatitis, and this "smelled" as if it could be a transmissible disease. Although, there were lots of other ideas about how this disease came about, and immunosuppressive effect if blood...all kinds of ideas. And we had a primate model, as well as the ability to study patients here. And so, we were ideally situated to investigate this very rare disease at the time, and of course, it turned out to be not so rare at all.

Joe: Yeah, I mean, again I think it's difficult for people for people who didn't live through that, and that was slightly before my career in transfusion medicine started (a few years before), it's difficult for people to understand the before and after. We could talk about this for an hour easily, but I guess, what I'm curious about from your perspective is: You've seen the before and after with HIV. How do you feel that that experience has colored the way we do things today?

Harvey: [00:08:58] Well, unfortunately it's colored it in a variety of ways, some of which are are good and some of which are bad. I'll tell you the bad first, and the bad is that at the time, blood centers around the country were involved in all kinds of developmental research. The advent of AIDS resulted in a lot of the research budgets being applied to regulatory issues. And so a lot of the centers that had been doing research were not doing research anymore, and that's a shame. The interesting thing of course, was that this was a brand new disease with an incredible 100% mortality at the time (or so we thought), and a long, silent period, and immune suppression such as we had never seen before. Here at NIH, where we had a primate model for post-transfusion hepatitis, we were able to take specimens from patients who had this rare disease, put them into the primates, and actually demonstrate for the very first time that whatever this entity was, it could be transmitted by transfusion. The other very interesting thing that we had here was the ability to look at twins, one of which had AIDS and the other of which did not. So they were discrepant for AIDS. And we actually did transplants from the twin who was healthy to the twin who had AIDS, and demonstrated that AIDS could disappear and the immunity could return. But then several months later, the patient became immune suppressed again. Again demonstrating, that in fact this was something that was transmissible, that was probably infectious. So these were exciting times, even though they were disastrous times for the patients who were infected.

Joe: Wow. You know, before we leave this, again, there's so much more we can talk about but we have a lot to cover today. There is one thing that has always bothered me, and I wanted to give you the opportunity to address it, and I don't know how to say this delicately, so I'll just say it: There has been in the press, and in movies and other presentations, some discussion that perhaps the blood industry or perhaps scientists in general did not pursue HIV as aggressively as they might have out of some sort of fear or homophobia or something along those lines, and I'm guessing you probably have fairly strong feelings on that, but I just wanted to give you the chance to tell me what those feelings were.

Harvey: [00:11:54] Yeah, and I feel that that's really a totally incorrect perception and I was here at the epicenter. It was really unclear as to what the cause of this rare disease was, and obviously we became very quickly knowledgeable that it wasn't rare at all. But there was a great concern that if one did the wrong thing, one could paralyze the entire blood collection system. And so, we asked for more data perhaps to demonstrate that this was in fact transmissible by blood than we would today, certainly. So, I would totally disagree that homophobia or fear of this entity had anything to do with the progress of the research. In fact, in many ways, certainly at NIH and at many other institutions, it was just the opposite. This was such an interesting phenomenon that you wanted to be sure that the tragedy didn't escape you, when just looking at this, again, brand new entity, something that had never been seen before, and when it appeared that perhaps a retrovirus caused it,

well, we all *knew* that retroviruses did not cause human disease. So again, these were things that it's really hard now to look back on and say, "Well, that was intuitively obvious," because believe me, it was not.

Joe: There is, again, so much more we could talk about with that, but I want to move on unless anything else you wanted to say about that before we move on, Harvey.

Harvey: Well, I think the only thing that I want to say is that clearly that influenced how we address infectious diseases from then on, certainly in the blood community, because as most people know, there were not only trials, but there were criminal trials for leaders of the blood community in many countries (not in the United States), but people were jailed because of their role in blood transfusion around that period of time. So, we are now extraordinarily cautious at even the thought of an infectious disease coming into the blood supply today. So that's been a total sea change in how we address risk and blood transfusion.

Joe: I would like to move on, Harvey, to our next point of discussion on historical stuff, because again, incredible things that you've seen and been through, and stuff that we take for granted today, such as the use of blood cell separators. That's fascinating to me that that hasn't always been around, because for all of my career it's been a part of what we've been able to do. But you saw the development of that a little bit before you got to NIH and a lot after you got to NIH. Could you take us through that a little bit?

Harvey: [00:14:45] Sure, let me tell you the story at the Clinical Center here at NIH, which is really an exciting story. There was a young patient, a 12 year old with acute leukemia, who was in the Clinical Center and whose father, George Judson, was an engineer at IBM. And Mr. Judson came down to NIH to visit his son, and his son, who was getting chemotherapy, was thrombocytopenic and leukopenic. And he came through the blood bank to see how we made platelets, and saw that we put bags of blood into a centrifuge and spun them down and collected platelets. He wondered why you couldn't hook the centrifuge up to a patient or a donor and collect cells from them, whether it were leukemic cells or cells for transfusion. And so, he put forth this idea to Jay Freireich, who was with the Cancer Institute, and IBM gave him a year of leave to come to the NIH, work with the Cancer Institute with Freireich and develop the IBM-MCI Blood Cell Separator, which was the first blood cell separator that used both arms; continuous flow, blood cell separator. And of course, it's been used for everything else since that time. I arrived on the scene just at about the time that this had been commercialized. Prior to that, people were making parts in their laboratories and putting them together and putting animals on these machines. And so, the rest in many ways is history in that we used it for plasma exchanges, and for collecting progenitor cells, and lymphocytes, and all kinds of things.

Now my own personal involvement, is again, an interesting one in that I had been working with Jack Latham at Haemonetics who had a discontinuous flow blood cell separator, the Haemonetics Model 30 that used one arm. I had read about two patients in South Africa with sickle cell disease, who had had red cell exchanges. The second patient became semi-comatose during the exchange. And so they published this experience, and said you should never do this in patients with sickle cell disease. You changed the 2,3-DPG levels, and the patients weren't delivering oxygen to the brain. Well, the beauty of being at NIH is that you could actually *study* that. And so, I got together with one of my colleagues from Johns Hopkins who was here at NIH at the time, Dr. Robert Winslow. We had a number of sickle cell patients, and in those days it was much easier. You got informed consent from the patient, you took your blood cell separator and you plumbed it any way you wanted. There were no controls or automated features, it was just a centrifuge and a couple of pumps, and instead of doing plasma exchanges or platelet collections, you did a red cell exchange. And so we did red cell exchanges in these patients, but we measured the oxygen delivery, and demonstrated that while the DPG levels went down and the oxygen dissociation curve shifted, the change in the viscosity of the blood was so profound when you put in stored blood cells compared to sickle cells, that oxygen delivery actually improved. And we went on to do a variety of other studies in this patient population showing that in fact, it improved oxygen delivery to a variety of organs.

So those were the first automated blood cell/red cell exchanges in the Western Hemisphere, certainly in the United States, but in the entire Western Hemisphere, and really popularized this treatment. Now as a house officer at Johns Hopkins, I'd stayed up all night doing *manual* red cell exchanges. Who does that any more? So in many ways, this was self-interest, I think.

Joe: (laughs) That makes total sense! Wow. I mean, and again, from those beginnings, the technology has changed. It's changed dramatically in a way, but it's still kind of based on the same principles that you guys developed there at NIH, right?

Harvey: That's exactly right. And we did a number of very novel things, some of which worked and some of which didn't work so well, but we presented them at national meetings. At a national meeting held by the Red Cross in Chicago, four of us got together and said, "You know, this business of blood cell separators and different diseases, we should form a society." An Englishman by the name of John Verrier Jones, who was actually a rheumatologist using plasma exchange in lupus, and Alvaro Pineda from the Mayo Clinic, who was doing a variety of things, and Duke Casperson from the Red Cross, and I formed ASFA [*NOTE: American Society for Apheresis*] there in Chicago after a Red Cross symposium on blood cell

separators. And again, that's become a very influential society in terms of advancing the cell separation technology.

Joe: To say the least, to say the least. Incredible discoveries and accomplishments! Again, there's a lot more that we could talk about there as well, but the next one is one that I that I really wanted to talk to you about, simply because I'm not sure I was aware of this before I started researching our discussion today. And that's simply this: You are, well, your blood bank is the original transfusion medicine service in the world! And I'm amazed at that! You were the one who first suggested in an editorial or in an article at least, in JAMA in 1987 I believe, that "transfusion medicine" was a more appropriate way to describe what we in what had been called prior to that "blood banking," were doing. Take us through a little bit what led to that thought process and what led you to, again, I know the phrase didn't completely originate with you, but you and your blood bank were the first ones to propagate it. So tell me a little bit about that.

Harvey: [00:21:17] Well, as I said earlier, I was a practicing hematologist and a clinician, and was actually attending on the hematology services several months of the year here at the Clinical Center, as well as, acting as the Deputy Chief and then finally, Chief of Blood Transfusion, and it occurred to me that "blood bank" was an archaic term. And so, I went back and looked up how it had evolved and what "blood banking" meant, and 1987 was the fiftieth anniversary of the American blood bank, at least what people considered the founding of the American blood bank in Chicago, and I thought that that was a term that was archaic. That we did much more than "bank blood." We went out and took care of patients, we did consultations, and so, I sat down with a number of my staff, and I can remember sitting in the cafeteria here at NIH saying, "We really ought to change the name of this discipline, blood banking just isn't sufficient." Harvey Alter was there, Rick Davey was there, Joel Solomon was there (who was the former CEO of the AABB; he worked for me for awhile). And we kicked around names, and the Russians used a term called, "Transfuseology" and that came up and we said, "That would be terrible! That would REALLY be terrible."

Joe: Thank goodness! [LAUGHS]

Harvey: Yes, thank goodness, we didn't do it. But then I remembered that I had talked with Tibi Greenwall a couple of years earlier and he told me that the Germans had a term, "*Transfusions Medizin*," ("Transfusion Medicine"), and I said, "You know? That really fits. The Germans do have a word for it. Why don't we use the term, 'Transfusion Medicine' for our department?" And that was the genesis of applying that term, which wasn't original with me, and the idea of writing that editorial in 1987 at the fiftieth anniversary of the American blood bank.

Joe: Well, I'm curious. How was it received?

Harvey: It's VERY interesting. It was not particularly WELL received. A number of pathologists, first of all, thought, "Who is this young guy, who is trying to tell us what we ought to call ourselves?" A number of the blood centers said that, "You know, you don't really include us appropriately, and after all, we collect all of the blood in the United States." And so there was a bit of a pushback, but then the Heart, Lung, and Blood Institute instituted a program for training people in “transfusion medicine,” and their influence, I think, really popularized the term far better than my editorial in JAMA which I think has been largely lost to posterity, except for your mention, thank you!(laughs)

Joe: No problem! I'm happy to pump that article! That's awesome! And actually, I was sitting here thinking as you were talking, you know, obviously my website and this podcast goes--I have the moniker "Blood Bank Guy" and I was just thinking, "I don't think 'Transfuseology Guy' would quite have the same ring."

Harvey: No! Thank goodness we abandoned that very quickly! And there were a couple of other names that were equally either pretentious or ridiculous and we had the good sense not to use them!(laughs)

Joe: (laughs) Good call, good call! Well, I want to close this part, kind of the "past" part of our discussion with something that moves from the past into the present, and that is genotyping, and the role of molecular testing in transfusion medicine that, again, is not new. It's been around for a while, but is starting perhaps to become, well, not just perhaps, it's starting to become more and more widely used. So, take us through a little bit of your experience with and your involvement in kind of the movement of transfusion medicine towards molecular.

Harvey: [00:25:34] Well, I had always thought, as did many other people, that in many ways, this was the first "personalized medicine." We actually did phenotyping, and here at NIH, we had, I think, the first computerized donor records where we had 20 antigens by phenotype and we could call in donors based on their phenotypic profile. And so, the idea of having personalized transfusion was certainly common to many of us in this discipline. The idea that you could somehow go a step further than the phenotype and actually do the genotype, which you would obviously only have to do once, and if you had technology, you could again, computerize this and not have to worry about having rare reagents that, at the time that we started here, we made most of our own reagents, whether they were reagent red cells or whether they were antibodies from blood donors. And we shared them around the country and frequently you couldn't get the cells or the antibodies you wanted. So, this was an example of, you needed the biology to advance and you needed the technology to advance. And one without the other was useless. And finally, you know the human genome project I think has brought this to the consciousness of many people we now call it, I guess, "precision

medicine" although, that's a little different than personalized medicine. The technology is clearly here, as is the biology. We know so much more now about the genes at the Rh locus and some of the other genes that aren't quite as simple as we originally thought they might be. Now, we, by the way, have just submitted a question to the FDA as to whether we can label our blood for the first time with the genotype, for the Rh-DEL, label it as Rh-DEL, and that, if approved, that would be the first labeling in the United States by genotype.

Joe: Wow. And again, that is a big change. So just, Harvey, for those that are just beginning in our field, can you give me a one minute what "Rh-DEL" means?

Harvey: Well, these are donors or patients who test Rh positive in one laboratory, and Rh negative in another laboratory and it turns out, that they have a very weak D. This comes up all the time. Patient or a donor comes to you and says, "You know, I'm Rh positive, but they say I'm Rh negative." And it turns out that this is a genetic change that results in a very small amount of RhD antigen being present, so much so that you find it serologically by "eluting" the antibody off of the red cell. So, "DEL" is "D-eluting" or "elution." That's the way it's gotten its name. But then, if you look at the genetic level, you know exactly what the genetic change is, and so you can label it without worrying that this laboratory test is incorrect or this other laboratory test serologically is incorrect. You can actually look at the gene.

Joe: I think that I'd like to transition, Harvey, if you're willing to go with me, into a little bit from that discussion, into more the present and where we are now, in terms of, you mentioned the whole personalized medicine, precision medicine, and I think it's really inarguable that in things like serology in blood banking and in transfusion medicine, we are getting more and more advanced. There's no doubt about that. However, I have heard and read things that you've said about your feelings on where we're going with how we do certain things, like for example, transfusing red cells, and I think it's safe for me to summarize your feeling in that your concerned that we're actually moving BACKWARDS in how we're transfusing, making the decisions to transfuse red cells. So, I wonder if you would take us through your feelings on that and perhaps, start from wherever you feel like it in terms of when you first got concerned about this, and what you see as the potential problem?

Harvey: [00:30:26] Well, first let me say that I think when we look at the product--the red cell, increasingly, we've had the technology to be able to characterize it so much better, that we're now able, if we wish, to match patient and donor at a very, very basic level, at the level of the gene, so that I anticipate that in the not too distant future, and some centers are already doing this, **all of our donors will be genotyped. All of our patients will be genotyped**. Perhaps, their entire genome, but at least at the red cell locus, and using the informatics that we have today, we'll be able to do much better transfusion in terms of the best match of red cell and patient.

But the other end, is of course, *when should you transfuse* and how should you make the transfusion decision? And, I think most of us who again are clinicians, believe that you should be able to select patients based on their disease and their clinical status, and determine when you ought to transfuse red cells. But increasingly, we're not doing that. More commonly, we're using algorithms, or we're using a "transfusion trigger." Transfusion trigger of 7 grams of hemoglobin or 10 grams of hemoglobin. I became concerned about this when the first paper came out talking about "liberal transfusion" and "restrictive transfusion." That was back in the 90s with intensive care patients, and people talked about randomized control trials. And I would say that, I don't believe there ARE any randomized controlled trials!

There are randomized *clinical* trials, but of all the trials of red cells transfusion, you will have to tell me where the control is. I don't see a control. A "control," to me, is the standard practice that someone is doing, compared with your innovation. Compared with, what it is that you're going to test. So, that if I were going to design a trial to see whether restrictive transfusion was superior to standard transfusion, I would want to take patients who are getting the transfusions as they were given back in the 1990s by the physicians at the hospitals where we were testing this stuff as the control, and randomize them to using a hemoglobin of 7 as the test trigger. Now, my problem is...

Joe: Harvey, I'm sorry to interrupt you--you mean as opposed to the two extremes.

Harvey: Exactly! What we have is, two relatively arbitrarily selected triggers: one is 7 and one is 10. There's been other trials where the number is slightly different but the concept is the same. Now, when I think about that, suppose, for example, that you had a dozen deaths in your "7 arm" and a dozen deaths in your "10 arm." and you'd say, "Well, they're equal. So, there must be no difference in using these as triggers." But that's not necessarily so. It may well be that in your 7 arm, you've restricted patients whom you would ordinarily transfuse. Elderly patients with coronary artery disease in distress, and you've given them 7, even though the standard of care at the time would *never* have been to restrict them to 7. Some of them perhaps died. In your other arm--your 10 arm, you may have relatively young patients who are ill, but had good cardiovascular status, good pulmonary status, and you're going to transfuse them even though ordinarily you wouldn't do that. But, that arm says “transfuse at 10,” so that's what you do. Some of them might die from TACO, from volume overload. So, they're dying from different kinds of things, and if you had given the older patient transfusion and the younger, healthier patient NO transfusion, then you might have had a better outcome with standard of practice than you had in either one of those. Now, I'm not saying that you would. What I'm saying is, that has never been tested. So we don't know, really, that restrictive transfusion is better in general than standard of care.

Joe: So, let me ask you this, Harvey, and I want to push back maybe just a little, because, I mean, I was practicing in the 90s, and I would say that I experienced---and this is totally anecdotal, I realize this---but, I experienced a ton of clinicians who believed in the old "10/30 rule," transfusing at a hemoglobin threshold of 10 g/dL or hematocrit threshold of 30%. And they, I felt like anyway, that my arguments about using other clinical parameters fell on deaf ears, in many cases. So, let me ask you this, how would you respond to someone that says, "Do we have any idea how clinicians (and I realize your background is that of a clinician! I don't mean to offend you with this), but do we have any data that suggests that clinicians actually DID use clinical information, other than the "triggers" before TRICC came out, for example, in 1999?"

Harvey: And this is the disturbing part because in fact, we did. So, actually Paul Hebert, who was the lead author on the TRICC Trial, surveyed, appropriately, and this was in Canada, surveyed clinicians. And the way he did this, is he gave them four different scenarios, and said, "What would you do under this scenario?" And one of them was again, cardiovascular disease. And what he found is that almost no one would transfuse the younger, healthier patient and almost everyone would transfuse the older patient with cardiovascular disease. So, while he didn't actually show that this is what they *did*, what he showed in a paper that was published prior to the TRICC trial, is that this is what they SAID they *would do*. So I think there were at least some data to suggest that people didn't use the old 10/30 rule, which by the way, is WIDELY misquoted. That was NEVER a rule and it was never put forth by the original paper, as a rule for all patients. What the rule was, if it were a rule, it said that if you have a patient going to surgery, and they're very ill, it might be prudent to transfuse them up to a hemoglobin of 10. That became the 10/30 rule.

Joe: Well, kind of like the 20,000 platelet rule was never intended to be a rule in the original paper, right?

Harvey: Absolutely. I think frequently, these are misquoted. And one of my former mentors used to say that, "If something is in the literature for 15 years, nobody reads it anymore." And it's true! And it's a shame because sometimes we get our ideas inappropriately from something we heard someone say when they misquote a paper.

Joe: Yes. Well, so you have recently published several things on your concerns about the trials in transfusion medicine, including an excellent editorial that was---forgive me, I don't have it right in front of me--but it was "Precision versus imprecision?" Forgive me Harvey, I can't remember exactly what it was called.

Harvey: Yes. "Transfusion medicine: precision versus imprecision medicine."

Joe: Thank you, thank you. And you also were involved in a paper with Dr. Deans as well, on the relevance of what you call "practice misalignments to trials in transfusion medicine." And I'm assuming that by practice misalignments, what you're referring to is transfusing people in a way that you wouldn't normally, according to the standard of care. Is that the correct summary?

Harvey: That's exactly right. And therefore, if you do that and compare two arms where you're transfusing people in a way that you wouldn't ordinarily transfuse them, then you really can't conclude that one is better than the other or even that they're equal.

Joe: Before we leave this, Harvey, I do want to say that I interviewed Jeff Carson last year for the podcast that was on Episode 23, I believe, and when I was discussing this with him, I asked him the question, "How should people use the AABB Red Cell Practice Guideline, the clinical practice guidance that had just come out." I said, "How should people use this?" And I thought Jeff's response was very illuminating. Jeff obviously, as you know, is a clinician as well, and he said, "You know what, Joe? They should be *doctors*. They should pay attention. These are just numbers, but the way that people should use this, should be to utilize all the clinical information at hand." I fear though, that what you're saying is becoming more true, especially as administrators get involved in the so-called "patient blood management movement." And I guess that's that's my concern that I wanted to let you elaborate on, Harvey. Are you concerned that all this data that's come out, all these trials that have come out, one just came out recently with the same two arms, you know, the same two extremes in cardiac surgery. Do you feel like we're in danger of misusing this data and becoming slaves to numbers and avoiding being doctors, basically?

Harvey: [00:40:45] I think that's exactly the problem and I'm even more concerned that the hospital administrator says to you, "Okay, we can save $230,000 next year by using very, very restrictive transfusion. Don't you think we ought to do that?" And so, instead of looking at our patients, we're looking at the budget. Let me just say, Jeff Carson has been a friend of mine for--I don't know how long, more than 30 years, and in fact, I was a consultant on Jeff's first trial---the orthopedic surgery trial. I suggested to Jeff at the time, that you have a third arm and that it be a standard care arm. And Jeff agreed with that, but it was funded by the Heart Lung and Blood Institute which said, " You get only get two arms. Pick two." My personal feeling, and I think Jeff's a terrific clinician, and I absolutely agree with him that you look at the patient and not the numbers, I think Jeff should have picked two other arms, but that's "water under the bridge."

Joe: If someone was trying to think of, you know, "How can I do a new study?" Where do we go from here?

Harvey: [00:42:00] A better approach, I think, is one that I recommended several years ago to the Heart, Lung, and Blood Institute. And that is, **I think more effort ought to be expended into looking at physiologic measures to predict transfusion**. Why don't we do that? I mean, we have such great technology today whether it's imaging or ultrasound. There have to be better ways than just looking at whether a patient is pale and whether their blood pressure goes down when they sit up, to determine when we ought to give a red cell transfusion. And, I think that we ought to be using, perhaps, a group of physiologic measures, compared to say, a transfusion trigger. And while I'm talking about that, let me just point out that in most of the studies using restrictive versus a higher hemoglobin, whatever that would be, many physicians would not enter their patients. Look at the number of patients who are screened and the number who are entered into the studies, and you'll be appalled and perhaps that's because they didn't fit the criteria. But perhaps it's because they didn't believe that their patients were being adequately treated by putting them into arms were the major determinant of transfusion was a single number.

Joe: Wow. That's sobering and I think really, really important information. Harvey, we have covered--we've talked about the past. We've kind of talked about past into present, now I'd kind of like to talk about present into future. And that brings us to, well really, that the paper that led me to contact you originally for this discussion, I realized shortly after we started talking that I wanted to talk about so much more with you, but I want to close our discussion with a paper that you published in October of 2017 in the New England Journal of Medicine called, "Crisis in the Sustainability of the U.S. Blood System." With your co-authors; Chris Hrouda and Jay Epstein. I think that this paper is one that has, in my world, I'm currently in "blood center world," has engendered a WHOLE LOT of conversation and really a whole lot of discussion on where we are in the U.S. blood system and where we're going. So, I would love for you to take us through what your thought process was for why the three of you wanted to write this paper and let's talk a little bit about some of the conclusions that you guys made as well.

Harvey: [00:44:40] Well, I'm delighted that it's caused some concern and discussion in the blood collecting community, but we had hoped that it might bring it to the attention of both the general medical public and the general public in general, but it hasn't caused as much interest from the public press as we had hoped. The idea here was that it has been known for several years now that as the red cell use has declined, the collectors of red cells have been increasingly under the gun in terms of their budgets. They're actually losing money, and most of the blood collectors in the United States are collecting at a loss, that is, it costs them more to produce red cells than they get from selling them to hospitals. Why is that? Well, there's a number of different causes, but the main one is probably the way they're reimbursed. Blood has become a commodity. People pay for it the lowest amount they can by having contracts that are competitive. That's not such a bad thing in

many areas, but what's happened is that if the competition is hyperacute, then people will try to sell their product below cost in order to "get the contract." What happens there is, of course, that first of all, you get into a "bare bones" type of system where you can no longer afford to have excess blood available for an emergency, because excess blood costs you money, and you can't afford that. You also can't afford to invest in improvements in blood because the first thing to go, when budgets get tight, is R&D. So, the idea of putting in new tests or of screening donors, say for, iron deficiency (which we know is a problem) and preventing it, or doing a whole host of other things, suddenly you can't afford to do that. Every time someone says, "Well, shouldn't you test for iron levels?" The answer is, "We can't afford to do that." That's a terrible answer! Or, "Shouldn't we be testing for Zika virus?" and the answer is, "Well who's going to pay for it?" So our system, unlike many other systems around the world, is under fire because of the way it's currently designed.

Joe: And, to what you just said, I would also add, Harvey, the other objection that you hear from blood centers is, for example, "Why haven't you implemented pathogen reduction technology?" "Well, is it REQUIRED? Hm." And the decision often becomes, unfortunately, as you said, because it's because of the financial implications when something is mandated, "then by God we'll do it!" And before that, "Well...eh." And that puts us all in a difficult position, don't you think?

Harvey: It does, and again there are several issues there, but I think a lot of people don't realize that---maybe you know? You know when the first test for HIV was developed and available?

Joe: Well, let's see...

Harvey: I won't put you on the spot...Oh go ahead!

Joe: I would guess 1982 or 1983.

Harvey: March of 1985. Do you know when it was mandated?

Joe:(laughs) Later than that!

Harvey: 1990.

Joe: Oh wow!

Harvey: So there was a five year gap. But, by the end of 1985, every collector in the country was screening blood for HIV antibody. So it's a shame that you can't---it takes so long to get regulations into place, that it's a shame that you have to wait for the regulation to do that. The other part of that, which I think is again, shameful,

is that, if the FDA puts in a regulation, the blood collectors all say, "Well, that's unfunded." Now the FDA doesn't have money to fund the cost of their regulation. They're looking for safety and efficacy, but if they put in a mandate to do pathogen inactivation then all the collectors say, "We'll all go out of business because we can't---who's going to pay for that? If we tell a hospital they need it, you know, they're still going to just compete on the basis of price and we're going to go out of business." So, it's really an interesting and unfortunate conundrum that the way our system is set up and the way our system is reimbursed, which I don't know whether people are familiar with this, but we're not reimbursed per unit of blood.

Joe: And, I know that that's surprising to people, especially people just beginning in the field. I mean, how is that possible? We send a unit of blood---a blood center sends a unit of blood out to a hospital, I know the blood center is not directly reimbursed from the patients cost of care, is the transfusion service reimbursed?

Harvey: [00:50:11] No it's not. Now, for example, if you do a procedure like a bone marrow transplant, you are reimbursed by the insurance company, a certain amount, a DRG, a "disease-related group" amount. So it might be $250,000 for the bone marrow transplant, and now the hospital has to figure out how to use that money best. And so, if they can cut down on the cost of blood, then they have more money for other things, including revenues over expenses. So they will negotiate with the blood center for a price for its blood which may not represent what it cost the blood center to make it. So the hospital doesn't get paid for the blood, they get paid for this big procedure, part of which is blood. And the blood center doesn't get paid for what the insurance company pays, it gets paid what it negotiates with the hospital.

Joe: And what's changed in recent years about hospitals' negotiating power?

Harvey: Well, hospitals have merged. We now have medical centers which have hospital networks, and it gives them a lot of bargaining power, and they've used it. And I suppose I would too, if I were in that position. They've used it to make blood centers, especially the smaller blood centers, compete with one another on price. Many have gone out of business or have merged. That's not necessarily a bad thing. I think our system had a lot of "fat" in it, and making it leaner and meaner is probably a good thing. But you can go too far, and if you start cutting staff, especially staff who would be collectors, it's much harder to “ramp up” than it is to “lay off.” And as I said, you also eliminate R&D and decrease education and decrease a lot of the other services, which will be seen as "fluff" rather than as important services if your cost is higher than your reimbursement is.

Joe: [00:52:24] So about a third of the people that listen to this podcast, Harvey, are international folks, mostly from Canada and the U.K. So, I'm sure that many of them are sitting there listening to our part of this discussion and saying, "Well, the

answer is obvious, guys! Right? Do what we do and have the government...have it all be centralized, the entire blood collection system." So, in your paper, I believe that you expressed some doubt whether that would be something that would work, or that would be able to be done in the United States. Can you elaborate on that a little bit?

Harvey: Sure. Well, I think that the United States doesn't have a single payer medical system, so I think it's highly unlikely that it would be very willing to accept a single payer system of blood collection and transfusion. There are other models, though, and I think if you start from the standpoint that you have to pay at least the COST of producing a unit of red cells, and add on to that the additional amount of money necessary so that you have enough ability to respond to emergencies, so you have some "surge capacity," and enough so that you can do some R&D. Then there are a number of methods which you can think about that could do that without having a single payer system. But, yes, countries like the United Kingdom and Canada and Switzerland, they have single-payer systems, some of which are governmental and others of which are not governmental.

Joe: So, in your paper, you also make several suggestions, including some of them that you've talked about. There's one I wanted to mention to you and get your feelings on, and it's kind of buried in there, but it's something that, I guess it hits me hard as being part of a blood center, and that's the "consignment model" of blood allocation, where the blood centers are actually financially responsible for the blood in the hospital whether it gets transfused or not. What's your feeling on that, and whether that's a sustainable model going forward?

Harvey: Well, I don't like that model, and it's a commonly used model for a variety of reasons. But what it means is, of course, that if the blood isn't used then it outdates for whatever reason, then the blood center eats the cost. That would be fine if somehow it could roll that into the cost of the units that are used. But, remember that the reimbursement for all the units that are used is based only on competition, and not on the cost of what's transfused plus what's not transfused, plus surge capacity. So, yes, I think instead of having the blood center at risk for whatever outdates, the blood center really needs to find a way to share that risk with its customers. It seems reasonable to me, but of course, that changes the way that blood is reimbursed.

Joe: Well, Harvey, I would really strongly recommend that everyone take a really good look at this paper. I'm going to put the link for it on the show page, again, that's BBGuy.org/045. And Harvey, I really think it's a very important paper, and I hope that maybe at least this podcast will get a little more discussion within OUR community going about it. Sadly, I probably can't help you a lot with the lay press. Sorry about that.

Harvey: That's alright! I hope it will, because we recently looked at the 2017 data (the data in that paper come from 2016), and unfortunately, the trend is the same, that the Red Cross, the largest collector of blood in the country, is still providing red cells at less than it costs them to prepare them, and America's Blood Centers, which collects most of the rest of the blood in the country, is running either slightly above the cost of producing red cells (1.5% on the average), but a large number of their centers are still in the red. That's not a good model for a national resource.

Joe: It is not. That is for sure. Well, Harvey, this has been remarkable for me. I am so honored again that you would spend an hour with me, and discuss all these different things that we've covered. Is there anything you want to leave us with? Any brilliant words of wisdom you want to leave us with?

Harvey: [00:57:00] I'm not sure they're "brilliant words of wisdom," but I want to let people know that when I got into this discipline many, many years ago, it was so exciting! There were new things happening: Blood cells separators, transfusion-transmitted infection that we could interdict. The only test at the time was a test for syphilis and agar gel diffusion for hepatitis B! We've come a long way! We're still there now. There are so many exciting things, with cellular therapies, with genomics, with information systems that can look at big data and analyze it. It's a time where, for young people coming into this profession, not only are you going to be able to really help patients who require transfusion and cellular therapies, but you're going to be able to make enormous advances! And I'd just like to encourage people to think of this as an exciting area of medicine and take advantage. Grab it by both hands!

Joe: That's awesome! Well, Harvey, thank you again so much! I am so grateful and so honored that you'd join me on the podcast today.

Harvey: You're quite welcome. It's been a pleasure.

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Joe: Not sure there is much of anything I can say to add to that, you guys! I hope that you understand that you've just heard from someone with more experience and wisdom than I probably will *ever* have in my entire life! You may not agree with everything Dr. Klein said, and I know some would argue with some of his thoughts about the "restrictive" vs. "liberal" red cell transfusion trials, in particular, but let me just say this: To use a baseball analogy, the man has lost *nothing* on his fastball! It's been such an honor to have him.

So thank *you* very much for listening! I've got some more good stuff coming, including a discussion on the top 5 changes to *AABB Standards* coming (that's in the next episode), an episode on Transfusion-transmitted CMV,

Bloodless medicine, therapeutic apheresis, and in episode 50, the return of the GREAT Sue Johnson to discuss the essentials of pretransfusion testing! I can't wait, and I really hope to see you soon!

So,until then, I hope you smile, and have fun, and above all, never EVER stop learning! Thanks a lot! We'll catch you next time.