Interview with Dr. Harvey Klein

Harvey G. Klein, MD, Chief, Department of Transfusion Medicine

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Interviewer: Katerina Vlantoni, PhD student, Division of History of Science and Technology, Department of Philosophy and History of Science, National and Kapodistrian University of Athens – NIH History Office pre-doctoral fellow (Spring/summer 2012)

Topic: Blood Safety in Transfusion Medicine

K.V.: I've read in many of your articles that you do have an interest in blood safety and all the issues of risks in transfusion medicine. What you mention in some of these articles is that there was a big change in the way that risks are dealt with in transfusion after the AIDS case. So, maybe you can tell me more about that.

H.K.: Certainly molecular testing in blood transfusion for safety was a result of the AIDS epidemic. So, going back to the 1982-3 when AIDS became upon the scene and gradually became recognized a transfusion transmitted HIV, before AIDS was known as HIV. Then in 1985 there were five companies that made ELISA type assays looking for antibody. And now you could detect antibody and you eliminated a vast number of cases of AIDS. But it was very clear that there was a window for the blood donor between the time that it might get infected and the time it might be antibody positive. And depending upon the kind of the ELISA assay you used well that window might be as long as 22-25 days. And while a lot of blood collectors thought at that point in time that the dramatic improvement in safety with HIV had come about, that was efficient. There were a lot of other people who said, well but you still have this window, you still have risk, you need to close the window. And the first thing that was done was a study of the HIV antigen, again a serologic test. And we were involved in a very large study, 523.000 samples over about a three month period. And we didn't really find any cases that were antigen positive and antibody negative. And this is important because even though there were no cases found you could predict that there would be a few if you did millions, and millions, not a lot but a few. Nevertheless, the FDA put pressure on the blood community to introduce that test. Which kind of brings us to 1994, when there was a meeting in this building, in the Masur Auditorium [and you are probably aware of that] and the commissioner of the FDA David Kessler essentially said 'you will do molecular testing'. And there was great reluctance to do that for several reasons. One of which was that blood banks, were very familiar with radio-immunoassays and ELISAs and all kinds of serologic tests. We didn't know anything about molecular testing. The second one was that there was really no good automated molecular test. It was one thing to have a small laboratory in the hospital and do a couple of specimens every once in a while, with a turnaround time of a week or two. And was quite different to do a thousand units a day and have to have a turnaround time of 12-24 hours because you wanted get blood back into the blood banks of the hospitals. And the third issue was that, it was very clear that

technology, as it then existed, was difficult to introduce because of issues of contamination. Blood banks weren't set up with the kind of laboratories that would allow them to separate extraction of DNA from testing. So, the blood bank laboratory people were very worried about this. But the FDA commissioner said you are going to do it. And I thought, and many people thought, that it couldn't be done. He can say whatever he wants, but it can't be done. But several things took place. One was at the Hurt, Lung and Blood Institute led contracts to seek… And it was as a direct result of the need as seen by the regulatory agency to close that window and improve blood safety. And the inability of any commercial company to really want to put their foot into that area, not knowing whether that was going to bring returns or cost a couple of hundred million dollars just do a standard assay and get it licensed by the FDA for screening blood. Licensing for screening blood is different than licensing for diagnostics. It's much more difficult to do. There two separate parts of the FDA that do it. And licensing as a screening test is much more laborious; it takes a much longer period of time to do and it's much much more expensive to do. So the HLBI led a contract and said however wants to apply to do this we will help you develop it, we will see this as a research. And Gen-Probe was one of the companies that decided that they would do it.

K.V.: So the contract was not directed to Gen-Probe immediately as they had this patent? You say Gen-Probe had to apply to get the award…

H.K.: They did. Although there are were only a couple of places they were really interested. And so, I think that, in all fairness, NHLBI probably helped them with their application as well as anyone else would be interested to do that, because they knew that they were interested and probably had the capability of do this as well as anyone. So it was a bit directed rather than just strictly led "let's see what you have and if your application doesn't look like you can do it, well we won't find anything". They were very very interested in funding something, and helping someone get this done.

K.V.: So, whose decision would be that at the NHLBI? Would be the Institute mostly or it was a cooperation with FDA, was there a common role?

H.K.: Really, no. It was really the Institute. Although the Institute obviously listened both to the FDA and the Institute had had a long history of interest in blood safety going back probably to the 1060s with hepatitis. Blood safety and transfusion transmitted infection had been a very large scientific interest in area of support to them. They supported the first studies in 1974-75 of transfusion transmitted infections where they started a repository looking for hepatitis virus, as obviously no one had any idea about HIV at the time, but storing specimens. We had a historical interest in this area. And as soon as they recognized that HIV was a major issue that there was a large unsolved problem they really stepped in and said we'll help support research in an area that it should be doable. The biology was easily understood and so it was a question of moving from a basic biology to the technology that could be used in blood collection centers, have a relatively few false positives and relatively rapid turnaround, and be able to be scaled up to large… But even then it was pretty clear that probably they couldn't test every unit. So the strategy was that they did at that point at time was to test pools.

K.V.: And how would you comment on this strategy, because by testing pools you would know that you wouldn't get as many positives you would get with testing individual samples.

H.K.: I thought, and many other people thought I think at the time, that eventually would go to single unit testing. It was clear that this was going to be difficult for a variety of reasons. And Susan Stramer has published a paper in 2004, I think, that gives a little bit of that history, in the New England journal, showing the closing of the window basically and giving a little bit of history of the pools. The Department of Defense went to single unit testing interestingly enough. Most other, certainly in the US, it was pools of 16 by and large, some pools of 24 and in Europe the pools were even larger. I think in Japan the pools were even larger too. But the Department of Defense went to single unit testing. And I always thought it's better to have molecular testing that you really feel comfortable about the technology even if they are pools because eventually you will get to the single unit. So, let's make sure we can do this even if it is not perfect. And it did gradually close the window, as you know, until today where even with pools the window is thought to be around 11 days and the number of units that have slipped through is tiny.

K.V.: So, what you mentioned earlier is that there was some reluctance in the introduction of these tests in the blood banks. You said that one of the issues was that it would be a problem for the blood banks to work with the new tests. How was the implementation after all? I've read some reviews stating that it was better than expected in the US.

H.K.: Yes, it was. But again, in some ways that is the blood transfusion people, in general, who I think at the second half of the 20$^{th}$ century were slow to change in general. You know what you know. And it wasn't just a change in test; I mean it was a brand new technology to them. Because they knew serology, and they knew serology whether it was ELISA testing, or whether it was radio-immunoassays… They felt very comfortable with serology. But they just didn't understand molecular testing and direct virus testing and PCR, of the varieties of PCR, and I think were a bit afraid of it. And since, once again, testing with a screening test is really quite different than a diagnostic test. They felt that even though there were laboratories doing diagnostic PCR that you just couldn't scale that up. So there was. The transcript of that meeting may be available [I don't know if you were able to find the transcript of that meeting in 1994. I don't have a copy but I presume it was transcribed because they were transcribing things back then]. I remember the commissioner getting up at that meeting and saying 'we are going to be doing it'. Really, without that statement, and David Kessler was a very opinionated and very strong commissioner. And I think without that real push forward, I don't think it would have happened so quickly. Eventually it would have happened but not that quickly.

K.V.: But until then, was there enough data to say that we have to implement it more quickly?

H.K.: Well, you know, again, it's always a risk-benefit issue. And having said that, I'd add that AIDS is different. So, that we've been very slow to add molecular testing to hepatitis B. Europe has been faster than we have. But even Europe was relatively slow because hepatitis was important, but was not HIV. HIV was something in many aspects, I think unique. At that time of course there was really no treatment, it was universally fatal. It was highly feared, in

part because it was a gay disease as the American public saw it and they didn't care that much in general about the gay disease. But if it was in the blood, then it was non gay people who could get be infected and the public was just really frightened. So you did things for HIV that probably the risk-benefit would not have pushed you to do for other diseases, even things like hepatitis. We would have been satisfied; we were satisfied, with serologic testing for hepatitis for a long time. Even though we knew that you could probably close the window a bit using molecular tests.

K.V.: So, that's why, as you've said before, the antigen test was implemented before HIV NAT test.

H.K.: Yes, I love that as an example. Do you know that study? [Yes] Harvey Alter was the first author. Because I thought it was a wonderful study, but to me it had two conclusions. First of all, there is a scientific interpretation. The scientific interpretation is: we found none and statistically that showed that the risk was 0 to 4, or whatever it was, cases per year. And then there is a policy which takes into account science, politics, public demand as well as cost-effectiveness. And if you looked at cost-effectiveness you would probably say it's not worth introducing. But public demand and policy and politics said it was going to be introduced. So really to me it was again… Antigen was such a small improvement in safety and I think the conclusion of the paper in the New England journal was that it was not worth doing. Certainly everyone who participated in the study felt that way, felt that way strongly. But policy takes into account science but science isn't the driver necessarily. And that was certainly a lesson that I was not prepared to accept at that point in my career. But after that study it became clear that that was the way policy was made. Scientists didn't have the exclusive right to say 'here are the statistics, and it's not cost-effective, or it's not worth doing'. This was something that the general public, who after all ended up paying for it, had a right to say 'we realize that it is not cost-effective but we want it'.

K.V.: But it is not very common that you would have a direct answer from the general public that would know all the scientific data and the other options.

H.K.: I don't think that the general public cared about the scientific data. What the public cared about was 'can you make blood safer?'. And if you can say 'just a little safer', they said 'but you can make blood safer, and it's HIV'. They said the same thing about hepatitis but not that strongly. But HIV was different. And even today HIV is a major driver. But not the way it was in the 1980s and 1990s. In the 1980s and 1990s there was a true hysteria in the US, which was in many ways ground zero for the epidemic.

K.V.: So, what you've said also with this study for the antigen that you didn't find any positive and then with projections and models you would say that there would be some positive.

H.K.: Yes, statistically based on the fact that 500.000 specimens is a lot but if you are collecting 15 million units of blood per year is so that much. So, you could project that you are going to find some positives.

K.V.: In the research after the 1990s on the transfusion transmitted infections most of the data come from modeling what would be your results. Especially with the NAT testing that there were no results yet, all was done with models. So, what do you think about this? This is also a change on the way you quantify the risks and do your work with the results you that have. How would you discuss the introduction of the models?

H.K.: I think it was very important. I was involved in some of the earliest studies. I was at the NHLBI between 1973 and 1975 and I was one of people who designed the so called TTV study, Transfusion Transmitted Viruses study. Originally that was supposed to be a hepatitis study, but James Moseley, who was one of the principal investigators from Los Angeles, I remember sitting in a room with a number of the investigators and Jim Moseley said 'Let's call it Transfusion Transmitted Viruses because it may not be just hepatitis'. Which I thought was very farsighted back then because everybody was interested only in hepatitis back then. And Jim said 'we ought to be saving specimens because there are going to be other viruses'. And we did set up a repository, of course at the time it was a serum repository because who know about NAT testing. So yes, blood became so safe that you couldn't do that kind of study anymore. That study was extraordinarily expensive by the standards of those days. There were several other similar studies that came along after that, including the antigen study. There were very difficult get off the ground because they were multi-centered studies. So it took a long time to design them, to get agreement. I can't tell you how long it took to get agreement from the various centers and investigators on how you are going to set up the antigen study. Then, it would take a fair amount of time to do the study. And then, of course, you'd have to analyze the study. And it ended up that if blood was relatively safe with the agents that you were looking for and these were relatively rare events your studies would have to be so big and take so much time that you'd never get them funded. And so the answer was 'let's take the data that we can get and let's figure out if we can model these issues'. Now, that's not to say that none of these studies are done anymore but they are just not done for that kind of risk. There have been studies done for West Nile virus and for Chagas disease, real lab studies. But by and large these are modeled studies because you cannot carry out the size and scope of that study any longer.

K.V.: So, do you think that this modeling (indirect estimation of the risk) has affected the way the residual risk was estimated during the discussion of the introduction of the NAT tests?

H.K.: It had no role at the beginning, I don't think, of NAT testing. I mean, once you got an idea with data from NAT testing, so you could make a model, that was important to continue to model. But at the beginning, I think, the test was going to be introduced and then we are going to get the data that we can get, not from a controlled study, but just from screening all the blood in the US. And so people started to develop models and then they started to see whether the data that came out was in concert with the models that they would develop and then gradually, as you've seen, they modify their modeling. But I think you are right, that was a total change in how we looked at measuring blood safety. To go to a modeling system and to convince people who weren't scientifically terribly estude that this was the only way you could look at blood safety from then on, that you couldn't do these studies. Because, frankly, a lot of reporters from newspapers said 'why don't you do a big study', 'what do you mean you calculated the risk, you need to measure the risk'. And it was very

difficult to explain, well, we can't do that anymore, there is not enough research money to do that. What we need to do is refine our models based on real experience data, even though the real experience data will just be positives in those people whose blood is not used. Measuring the outcome in people who are infected because you missed, that are what you are going to model for based on the number that you get in the sensitivity and the specificity of your assay.

K.V.: So, were the data that came out from all these modeling methodologies accepted from all the research groups at that time, at the beginning of the 1990s?

H.K.: I think the concept of modeling was very rapidly accepted. Different groups had slightly different models, and there were some debates as to whether the model was taking appropriate things into account or how you looked at that. But there wasn't great reluctance either to rely upon modeling or even the people who had slightly different models, there wasn't enormous controversy about 'your model is no good', it was just that 'my models are little better'. And that is, of course, important because in many instances scientific arguments are 'yours doesn't work and mine does'. But that was not the case here. The case was 'mine is a little better, a little bit more accurate than yours in predicting what the outcome is'.

K.V.: From what I've seen in the publications that I've read until now, is that there is a lot of cooperation in the US regarding the issues of blood safety. There are many co-authored papers from you, researchers from the Red Cross or other blood banks. There is cooperation…

H.K.: Yes, and I think there was cooperation even before the AIDS epidemic but not to the extent that there was after the AIDS epidemic. And again there are very few silver linings on the AIDS epidemic, but one of them was certainly in blood in the US. That all of the collectors cooperated with one another and information that previously might have been considered proprietary suddenly was shared because it was in the public good. And obviously that is a good thing but it doesn't always occur. But for AIDS there was absolutely no question that investigators in the Red Cross, investigators in what is now Blood Systems Incorporated (which was United Blood Services I think back in the 1980s and 1990s), investigators were not only cooperating but they were personal friends and, as you said, the multi-authored publications, everybody who could participate was willing to share data, analyze data and cooperatively share the problems they had with their own testing. Which again was something that was really new; no one wanted to say 'you know I am having a trouble with our test, we are having so many false positives or one of our centers is having problems'. No one wanted to share that king of data both for reasons of proprietary issues but also for legal issues, liability issues, you didn't want to say 'Well, I am having some problems'. But, all those data was shared, so that was a good thing.

K.V.: There was also this argument, in some of the first articles about the introduction of the genomic detection that said that these tests would be added to the serologic tests. Therefore it will not save us any money because we will not stop doing tests previously done. Was this an important argument at the beginning of the introduction?

H.K.: Well, again not so much for AIDS. People have always asked that. Well, where are we going to get all this money? Is there something that we can eliminate? And really, to the best of my knowledge, in the US at least, the only test that was ever introduced, licensed and then withdrawn was the HIV antigen test because it became obvious that was not adding anything after you had a genomic test. But other assays, even if they just added a little bit, are very hard to remove. And of course, we still test for syphilis, which was introduced in the 1940s and probably does absolutely nothing to the blood supply. It is very difficult to eliminate a test. The paradigm of potentially making blood less safe is one that the regulatory agency has a great deal of difficulty with. So, once a test has been approved you have to provide them with almost ironclad data that removing that test will in no way make blood less safe. It is very difficult to remove a test. So, yes, that argument is… Though is some places, of course, NAT test was not introduced in Europe, again they didn't have quite the experience in some of those countries that they had in the US with the politics, the legal issues. And, of course, the risk was somewhat smaller, so by their models it would have added less if anything to the measurable safety of blood. In the UK they were very reluctant to the NAT testing.

K.V.: Now that you mention about different countries, in the case of Greece, that I do study the introduction of NAT as part of my PhD research, there was not a lot of research about modeling the yield of NAT testing. But there were some discussions among blood bank professionals saying that there are other risks to consider and we cannot all the time follow this technology driven model by introducing more and more tests.

H.K.: Well, one issue of course is what is the frequency and the population, so what is both the prevalence of HIV and what is the incidence, whether there are new cases. And US, of course, especially in certain areas of the country and socioeconomic groups in San Francisco, New York city, Miami the risk was so great compared to rural areas. But in US you can't say will do this with for the state of Florida, you have to do it for the whole country or nothing. I do not know how that is in Greece, but the prevalence in Greece was much lower and the incidence was also much lower. So again you could say, in terms of cost-benefit, I'd rather immunize kids for measles than introduce HIV testing for blood with NAT.

K.V.: So, in the US all this discussion about being able to give this money to alternative solutions even in transfusion medicine, to advance transfusion safety and not blood safety, to do other interventions in the hospitals about risks that are greater as the data shows for risks in transfusion. How serious were these arguments?

H.K.: A lot of people said that we are doing the wrong thing. Again we are addressing with technology a relatively small risk when we know that there are larger risks. Why aren't we upgrading our computer systems, for example, so that you can't give the wrong blood to the wrong patient? We can measure what we are doing there and it looks like it's a much bigger risk than HIV, what remains of HIV, why aren't we going that? And again I think the answer was that HIV was different. Really was a totally different animal. Yes, people got very upset if you gave the wrong unit of blood and you killed someone. But they were dead. If you infected them with HIV, they were alive for a long time to remind you that they were going to die. And, people really were terribly afraid. I mean, it's hard to appreciate the level of

fear. We had people who donated blood, who wouldn't come and donate blood because of the fear of HIV. Even though you explain to them that it is not the people who donate it, is the people who receive. But the level of fear was in some ways akin to mad cow disease today in the UK. I mean, it really was in some ways a hysteria. There were people who refused to receive blood transfusions, just refused to receive them because of the risk of the HIV. Or you could say we can now tell you that the risk is 1 in 250.000, 1 in 1 million, 1 in 2 million, they did not want blood because it was HIV, not like it was hepatitis or Chagas disease or West Nile virus, it was HIV. So it was different.

K.V.: What I find interesting is that even after 1999, that the test had already been introduced as investigational drug; there were still some discussions from people publishing articles discussing these issues that the money could have been spent somewhere else or that there is low cost-effectiveness ratio, and all these things.

H.K.: Yes

K.V.: So, was there a 'real' discussion going on?

H.K.: Well, when you say a real discussion… Yes, there was a real discussion, there was in the literature. No one seriously thought that you were going to stop testing. Or, even that you are going to stop refining the assays to get… The assay we use now is quite different than the assay that was originally used. I mean, certainly, refinements have taken place in assay technologies since the original introduction. You could make that argument but no one seriously thought that they were going to remove NAT testing in the US. That wasn't going to happen and isn't going to happen. Now, I think the other argument that I always made, whether is a good argument or a bad argument, is that you can say that this money will be used for other areas of blood safety. And you can say it might be used to immunize children against Polio or whatever, things that are clearly cost-effective. But in point of fact it probably won't be. It's going to be used for this because the public is demanding it, or it will probably be used to something else that the public demands that might have absolutely nothing to do with safety of health. You know it may have something to do with gasoline, or you know farm subsidies so that corn is cheaper. So, the economists make these articles and the cost-effectiveness people make these arguments, and they seem to make sense. But in practical terms it doesn't work that way. That money doesn't get used for other areas of blood safety or even possibly even health, probably not blood maybe health, but maybe not even health.

K.V.: At that point when the two technologies, TMA (Transcription Mediated Amplification) and PCR (Polymerase Chain Reaction), were being developed at the same time from the different companies, was there any discussion that one of them might be better? I haven't seen a lot of discussion…

H.K.: There were discussions and even there were publications about the sensitivities and the specificities. But, one of the practicalities was that if you had equipment from one company that you were using to something else then you might want to use that company's test. If you had a big contract, with Roche for example, for something else, then you might want to use their technology even though there might be some slight differences reported in

the literature in sensitivity or specificity. So, there was no serious discussion. The other concern always is, and I think this historically has been a valid concern, what happens if one of those companies has a problem and it doesn't have reagents. You have nothing. What happens if you only have one company and they decide to charge you ten times as much. So, it's good to have competition. And I think all of those kind of played into it although these were not strong arguments, but whenever you talked about it you mentioned these kinds of things. So you really didn't want just one manufacturer.

K.V.: This beginning of the NAT testing in the blood banks was it also driven from the fact that on the plasma industry NAT was introduced beforehand, at least in Europe, especially in countries that did produce that technology, like Germany?

H.K.: Yes, in a way I think that played a role. First of all, it demonstrated that it could be done. Maybe, in not quite a scale that you are going to have to do it to blood collection in the US, because the plasma industry has far fewer collections. But first of all it demonstrated that it could be done. And second, I don't think the not-for-profit blood collectors wanted somehow to be outdone by the for-profit plasma collectors and fractionators. So, yes I think that did play some role. Although, one again, I feel that the major issue was that the commissioner of the FDA said 'you're going to do it'.

K.V.: That was also a difference with Europe. In the US NAT testing started for the HIV virus, which as you said was driving the changes. But in Europe, in the plasma industry, it started with testing HCV, because of many cases of contamination.

H.K.: Yes. But I think it also changed the testing paradigm. Now that you get new agents the first thing you look for really is a NAT test, even before you look for serology. So, that is sort of a new way of thinking about it.

K.V.: There are some discussions, in parallel, that introducing so expensive tests makes the difference even bigger if we see it in a global scale. I've seen some arguments concerning this, but again you cannot do much about this.

H.K.: Well, again I think in some ways it's a risk-benefit. If you have a very very cheap serologic assay in a country where you have a prevalent infection but now the incidence isn't rising then maybe it makes sense just to use your immunoassays because NAT is too expensive, serology is cheap. Nat is difficult to do, serology is easy to do. So, in some ways let's take the step that will make the blood more safe even if isn't perfect. People say in the US the perfect is the enemy of the good. So you do the good, because you really can't do the perfect, can't afford the perfect, you don't have the technology, or even your equipment breaks down and you have no one to fix this. You can fix your fairly simple serologic assays. You can't fix your NAT, you don't have the engineers, where are you going to get them in some developing countries. This is real problem. This is why in Africa, for example, Jean Pierre Allain has a paradigm where they use rapid tests for the donor. Because of the prevalence of the disease they don't even want to collect that unit of blood so they'll test the donor with a rapid test prior to donation. If they are positive they send them to a clinic and they don't collect the unit of blood. Which, again, I think is a strategy that would really work in the US but it probably makes a lot of sense in some developing countries. Those

assays are cheap, they are not automated but they are easy to do. And if you have a high prevalence it makes a lot of sense.

K.V.: You said that the introduction of NAT tests did make a difference on the way the laboratories are set in a blood bank. What other difference do you think it made in the field of heamatology and in the blood banks?

H.K.: Of course, it changed training of medical technologists who were not oriented at all toward molecular medicine. Their training had nothing to do with molecular medicine. And suddenly, being forced to introduce a molecular assay; suddenly they began to learn about molecular medicine which turned out to be important in other areas of the blood bank, which we can talk about at the end if you like. I think that was another change in how you taught people; it broadened their scientific understanding in general, because now they had to think about DNA and RNA.

K.V.: So, for blood banks also there is this move towards biotechnology that is affecting many fields in medicine.

H.K.: Yes, we've talked about testing for infectious disease but there was sort of a parallel going on in some blood centers and some hospital blood banks which was the HLA testing, and introducing molecular testing there. Which came about, I think, in the late 1980s. And this was a function by and large of donor transplantation, in the national marrow donor program. And again, sort of an interesting story, because HLA testing was all serologic, it was the Terasaki assays and serology. When unrelated bone marrows became a real possibility in the so called National Marrow Donor Program and NMDP was set up in the US, and that had to be the mid '80s, it was 1986, it became obvious that the matches that we were doing weren't very good matches. Probably because the assays weren't very good assays. And so, they pushed a lot of money, in part supported by the Department of Defense, into molecular testing of HLA. And because they were a national program with multiple centers and had a lot of money, and required the participant to do transplantation to get unrelated bone marrows, or stem cells later, but bone marrows then, you had to be able to do molecular testing. And they helped you by paying for some of it. Suddenly a lot of places, that otherwise at the beginning did just serology, suddenly found themselves required to do molecular testing for HLA. And the change from serologic testing to molecular testing was incredibly rapid and was really driven by the National Marrow Donor Program (NMDP).

K.V.: This is very interesting, because I've found a lot information regarding attempts to develop molecular testing for bone marrow program but I didn't know that it was so connected with the development of molecular testing.

H.K.: That was what really pushed it, first in the US and the worldwide. Because we had the largest registry, so for European countries that wanted to become collaborators they had to introduce molecular testing too. And again, some historical interest: why was this supported by the Department of Defense? Well, the usual reason that is given is that the Department of Defense was concerned if there was a nuclear war, you would have to transplant people, so they were interested in bone marrow transplantation. But, the real reason was that the Admiral Zumwalt, who was chairman of the Joint Chiefs of Staff, "Bud" Zumwalt, and had

been the one who called in the Agent Orange in the Vietnam War. His son died of a lymphoma, probably as a result of Agent Orange, he had a bone marrow transplant, eventually failed and he died. Zumwalt became very interested in bone marrow transplantation. He was a very very interesting guy, very bright. And he was lobbied by another man, whose daughter had died after a bone marrow transplant that was unsuccessful. It was Zumwalt's connections with the Department of Defense that got the money for the National Marrow Donor Program. They put a lot of money into it. Without them it probably wouldn't have gotten off the ground or would have died in the first three or four years, but they continued. They're still putting money in, but at that point they were really the souls support for that program, they put an enormous amount of money in. And it's funny how those kinds of things can change technology. Because NMDP changed the technology across the country for HLA testing, not that it might not have changed subsequently but it certainly changed a lot more rapidly than it would have. And that happened because of Zumwalt and the Department of Defense.

K.V.: This is very interesting; I didn't know all these connections.

H.K.: Yes, it is interesting. And Zumwalt was for a while chairman of the Board for the National Marrow Donor Program, he was at the Board of Directors.

K.V.: I was reading in an article that the introduction of NAT might also result in some ethical complexities. What ethical complexities could come in the screening program for blood banks?

H.K.: One issue is if you are saving specimens. Because, some blood banks began to save serum and plasma, after the AIDS outbreak, in repositories so they could go back and test. With NAT testing, people wanted to save cells, and now you had DNA linked with large populations by name. So, yes, you can test them for infectious agents but you can also test them for a lot of other staff. So, saving it, all of a sudden, you had to have your informed consent what it was going to be used for or what it wasn't going to be used for. Or you had to unlink the specimens. If you unlinked them, now you knew something about the specimen but you couldn't figure out who it came from. Now you could do testing of blood donors, but you couldn't go back and find the donor who was positive for anything. So you had the choice, either had to get an informed consent or you had to unlink the specimens so that no one could then go back and say: 'we just happened to be looking for other genes and in your specimen we found that you have such and such…'. So, you can't do that.

K.V.: I think we've talked about most of the things that I've noted here. I would like to ask you a last question regarding the issues of risk in general. [specific questions to me research project]. In one of these articles for the REDS study, from 1996, the famous article from 1996 that describe the model about the infectious diseases, at the end they state that 'the decision about implementing NAT test will be difficult', when the article was published in 1996. But it seems that at that point it was already almost decided that the tests were going to be implemented. So, I am thinking that when I first read this article, and saw that it was very important and very much cited, the end that it says the decision will be very difficult because there are many demands and it's not cost-effective, to me was that 'ok, there has to be a lot of discussion', but then I saw that the test really started to be implemented and

most of the articles that cited this article said that this article shows that we have to implement it. So, I was thinking that maybe for doctors and the people in the work of transfusion needs a different interpretation.

H.K.: The people in transfusion didn't want to introduce this. They really didn't. The very few, and I thought it was important, but everyone said "you are the National Institutes of Health, you are a research guy. You are not in the real world; you don't understand the problems to real world. You do a few collections a year, you collect 10.000 units a year, and in our blood center we collect 800.000 units a year. You don't have any idea what this would involve". There is some truth to that. There was great reluctance. Eventually, as I said, blood bankers tend to be slow to introduce new technology. They have to be dragged kicking and screaming and I think eventually they would have been dragged kicking and screaming. Probably ten years later, when the technology was being used in other areas, and using TMA and PCR would have been much easier to. But no company would have developed it if they didn't have a commitment by the blood transfusion community to buy all of these tests and the blood community was absolutely dead set against it.

K.V.: What you say in one of your articles about safety in transfusion is that: maybe the issue at last is how we can define 'acceptable risk'.

H.K.: Yes, and I guess I've become very cynical about that, because AIDS was different, but blood appears to be different too. And a lot of things that you just wouldn't do in other areas because of cost-benefit, you do in blood because its blood. And, because it's a risk that people, in some ways, are forced to undergo. Even people who ride motorcycles, and won't put on a helmet because it's their choice, want blood to be absolutely safe, perfectly safe. Because they don't elect to take it, they are forced to take it or die. So, they want that particular risk… It's almost impossible to say what's an acceptable risk. People want it to be perfect because it won't be, it will never be perfect, it's biologic. So, I don't know if they will ever define acceptable risk in blood transfusion.

K.V.: And the zero-risk objective came also after the AIDS epidemic?

H.K.: Yes, it did. People were willing to accept some risk of hepatitis. They were willing to accept some risk of getting the wrong unit of blood. It really didn't excite the general public; they didn't like it of course. You want to be confident you are going to get the right unit of blood; you want to be confident that you are not going to get hepatitis. But, you weren't banging your congressmen's door down about it. With HIV it was different, you were banging, and you were marching in the street. So, then people started writing about what's an acceptable risk, why we can't get zero risk. And it doesn't matter, we can't get zero risk, but still the general public will demand more from blood than they will from anything else. Having said that, and also I'd say that blood is pretty cheap. If you ask my colleagues they'll say I am absolutely wrong about this. Blood is pretty cheap compared with a lot of other things that we do. If you walk around here in the morning and someone goes to see a patient and they have a headache so you order an MRI. It's a thousand dollars, 1500 dollars, they don't even think about that, send them down for an MRI. A unit of blood is a couple of hundred dollars, it is not 1500 dollars, it's relatively cheap. But compared to what it used to be, because of how blood started out, that was really very cheap and it's donated and ought

to be free. So, by and large, blood compared to what it does and many of the other medical treatments is actually pretty cheap. Even with all these things we've added on over the years, again compared to the some of the other things that we do. But, because of what it used to cost and because there are 15 million of them transfused a year across the country. How many MRIs are done? You don't think about that, you don't say 'we can't order an MRI because there are 8 billion MRIs done and it's going to cost so much money to do an MRI'. So, I think blood bankers think differently about blood than radiologists think about MRIs. Blood bankers think there are 15 million of them and we can't afford to add a dollar to that because its 15 million dollars to the health budget and my hospital won't pay for it. But in point of fact blood is pretty cheap as a treatment, and the hospital will pay for it, they won't like it, but they will pay for it. If the patients say they want to be safer, the hospital will pay for it.

K.V.: One of the most interesting arguments about the issue of blood safety and how it has changed over the years is that maybe we should consider risk in different ways, like blood availability which could be a risk issue.

H.K.: It is a risk issue, absolutely. Well, I've made that argument over the years but the point probably isn't that availability is clearly a risk. But we collect a relatively small number of the medically eligible blood donors in the US and you see during 9/11 so much blood was collected and had to throw it out. The blood supply isn't infinitely expandable; there isn't an infinite amount of blood that can be collected. We could collect a lot more than we do now, and there is always a question of whether we are just collecting enough for the use. Because obviously you do not want to collect a lot and have to throw it out. So, availability is an issue but I don't think that infectious disease testing is really the issue that limits blood. We do eliminate a lot of donors, a lot of the easy donors. We used to say in the hepatitis world where you had false positives: the more you came in to donate the more likely it is that you have a false positive, and eventually be deferred from donating blood. So the best donors were the ones most likely to be permanently deferred, because eventually they are going to get a false positive test. Now the tests are better, so it's less likely. But you can always replace that donor with another donor, right now that's not a limiting issue. It's something you have to think about, especially with rare blood groups, that you don't want to have tests in there where you are going to have false positives, to have to remove people. But we do a lot of crazy things. We eliminate people who have been in the UK for a period, where the risk is almost zero. We still don't collect from people who have a family history of Creutzfeldt–Jakob disease, what's the risk there? Probably zero. So, there are a lot of crazy things that we do that you can increase supply. So, I don't think supply is a major issue. But it is a risk, and certainly for rare units you don't want to eliminate those donors.

K.V.: I know that now you are also doing research regarding the pathogen inactivation methods. At that point, in the '90s, it was also argued by some people 'why do we invest so much in the NAT technologies since we won't use them in a few years, or a bit more, because we will have pathogen inactivation techniques'. So, why to pay such an expensive technology for a short period of time.

H.K.: Yes, I think that's still an argument. But as you can see in the US we don't have any pathogen inactivation. In Europe they do. But, I would point out that in Europe they are still testing all of their blood. And if we introduce pathogen inactivation in the US there are very few tests that we'd eliminate. We'd probably still continue with the tests that we are using, that's sort of the paradigm. We do our studies on blood that's already been tested, so for that reason you wouldn't remove many, if any, of the tests. But it may prevent you from introducing new tests. So, for example, we know that the pathogen inactivation technologies that are currently being tested and the ones that are being used in Europe are very effective against West Nile Virus. And I suspect that if we had had those pathogen inactivation technologies in place when West Nile came along, firstly I don't think we would have seen West Nile, we wouldn't have seen it transmitted by blood because the agent is so sensitive. We wouldn't even have known that it was a risk of transfusion. So I think it would eliminate new tests but probably you are going to keep most of the tests that you have, because your studies would be done with blood that is tested and leukoreduced. Therefore the license for the technology would be applied to blood that is tested and leukoreduced that way it is now, that would be the license. You'd have to run another study, which would be impossible to do, against blood that is pathogen inactivated and tested the way we test it versus blood that is pathogen inactivated but isn't HIV tested. No one it's going to allow you to do that study.

K.V.: So, what do you see in the future?

H.K.: I think pathogen inactivation has to come. We are using NAT for plasma and for plasma fractions and there hasn't been a case of HIV, HCV, or HBV in the hemophiliac since 1987, in adequately treated factor viii or factor ix fractions. So, I think pathogen inactivation has to be the way to go, it just has to be. I assume that will happen. I think we will get a lot more data out of Europe and maybe other areas of the world. The US FDA seems quite reluctant to introduce pathogen inactivation.

K.V.: Why do you think the FDA is so reluctant?

H.K.: Because blood is pretty safe. And because you have to treat everything, probably, and they are very reluctant, I think, to add something to the unit of blood that everybody gets, including MNH, children, and pregnant women. There are very reluctant to add something that might have a toxicity ten years from now. And so, they are making the hurdles in the US almost impossible to get over in my mind. And I think, perhaps, when they see a lot of the data from Europe eventually it will happen and then the technologies will get better. The current technologies are so like the first tests, they are kind of crude but they will get better.

I just want to make one other point that I think is important. The introduction of genomic testing with first, probably, the infectious disease if not first, the biggest impact, and second with HLA, has now made blood collectors much more comfortable with this kind of technology. And so, introducing red cell genomic testing, I think, will go a lot faster. And eventually that is going to be the way; we won't use serology any longer. That will be wild. Now centers that would never have considered doing this, unless they already had equipment and experience with infectious disease testing and HLA testing, very rapidly have introduced red cell testing as well.

K.V.: So you think at some point serology will diminish?

H.K.: If not totally disappear, it will be become very unusual. Because you'll probably test every blood donor, you will have to test them once because genomic testing doesn't change. And you'll be able to test them very cost-effectively, I believe, because you are going to have large chips that will do everything. And you will probably test every patient, and you will probably be able to do it very rapidly because the technology is such that really lends itself to high throughput chips and large numbers of assays and high throughput and that will end up being pretty cheap. So, I think we are going in that direction where our blood donors will all be genotyped and our patients will rapidly be genotyped for red cell antigens, probably platelet antigens as well. It's easy to do. Once again, many blood bankers are kicking and screaming about that now, and saying it's never going to be cost-effective. Other places were doing it, New York Blood Center, Puget Sound Blood Center in Seattle, Blood Center of Wisconsin. They are already doing it; these are not licensed assays yet, so they can't really label the blood that way. But they are doing it. And because they are doing it manufacturers are interested because they see a potentially large market. Not as large as other markets because you only have to do it once. So, I think eventually, because it can be easily automated and because now we sort of understand the concept of the new chip technology that is going to come as well. And I think that will again be in part a legacy of the AIDS zero and NAT testing of infectious disease. We will probably be testing everything that we do as long as there is blood that has to be compatible. […] The other thing that obviously is important in blood collection centers is that we have big time information systems. And again that fits well with this kind of technology; it will fit well with red cell molecular testing as well. You have to have capable information systems, they have to be reliable, they have to be able to handle large amount of data, they have to be rapidly recoverable, we have that.

K.V.: Thank you very much!