This is an interview with Dr. Harvey G. Klein, Chief, Department of Transfusion Medicine at the Warren Grant Magnuson Clinical Center at the National Institutes of Health, Bethesda, Maryland, on 29 January 1993. The interviewers are Dr. Victoria A. Harden, Director of the NIH Historical Office, and Dennis Rodrigues, Program Analyst. The subject of the oral history is the NIH response to AIDS.

Harden: Please start by giving us a brief summary of your education and career up to the time that you became aware of AIDS. I would also like you to comment on why you decided to go into medicine and medical research.

Klein: I went into medicine probably because my uncle was on the faculty of the Harvard Medical School. He was a pediatrician, and throughout my childhood he was more or less a role model for me. He was my great uncle. He was one of the first professionals in the family, and that motivated me to look toward medicine. But, as an undergraduate at Harvard, I was a german literature major. I simply did enough science at Harvard, and at MIT (Massachusetts Institute of Technology) to satisfy the requirements for entry into medical school.

When I went to medical school it was with the object of becoming a physician, but not necessarily a researcher. I do not think that I, as a graduating senior from a liberal arts college, really knew what the various opportunities were, and what they meant, in medicine. But, looking at the various medical schools available and the geographic area that I wanted to be in, I applied to, and was accepted by, the Johns Hopkins Medical School. As it turned out, Hopkins was one of the most research-oriented medical schools, if not "the" most research-oriented medical school, in the United States. As a first-year medical student, there was an elective period, and during that elective period, I became interested in research, beginning with a small project in a laboratory at Hopkins. From that point on I felt that that was more or less what I wanted to do in medicine. I wanted to see patients, I wanted to practice clinical medicine, but I wanted to be doing something that brought new information to the medicine discipline.

I spent four years as a medical student at Hopkins. I was interested in internal medicine, so I stayed in Baltimore to be on the house staff at Hopkins. It was the house staff named after Sir William Osler, and it had quite a long tradition of clinical investigation.

While on the house staff, once again, I think my decision to go into the blood area was molded by an individual who was generally considered to be one of the best clinicians at Johns Hopkins. That was Dr. C. Lockard Conley who, as it turned out, was the Head of the Hematology Division. He was my attending physician and my mentor, to some extent, and was very much oriented toward investigational studies. No matter what you did, whether you were a private practitioner or a full-time clinician at a

medical center or a laboratory researcher, Dr. Conley always thought that you ought to think in a research mode, make and record observations, and try and interpret them.

After my residency I became a fellow in Dr. Conley's division. This was at the time of the Vietnam War. Hopkins had all kinds of close ties to the National Institutes of Health. I had actually already applied to the Commissioned Corps of the Public Health Service and had been assigned as a senior medical student, as a first-year intern, and as a first-year resident, to the Centers for Disease Control in the Infectious Disease Division, Venereal Disease Branch. I had been to Atlanta and looked around. It was only when I decided to go into hematology that I thought that perhaps studying venereal diseases for two years of government service was not in the best interest of my career. I talked to Professor Conley about it. He said, "Why don't you see some people at NIH," and he gave me the name of a Dr. Ernst Simon. Ernst Simon was the first Director of the Blood Division of what was then the National Heart and Lung Institute. He had just arrived. I think he arrived in April of 1973. I was scheduled to enter the Commissioned Corps on 1 July 1973. I interviewed with him. He had very few physicians working for him—certainly no young hematologists—and he said, "I would be delighted to have you with Dr. Conley's recommendation for two years in my division." So I came to the National Institutes of Health, in the Blood Division, for two years after my hematology fellowship at Johns Hopkins.

Harden: As a part of the Commissioned Corps?

Klein: As a part of the Commissioned Corps. I was one of what was then called the "Two-Year Wonders." I had thought, since it was an option at that point in the Commissioned Corps, that I would probably stay for three years. The program, as it had been outlined to me, was part administrative, but the Intramural Program had been described to me and I had actually gone over and talked with Dr. W. French Anderson at the time. Dr. Arthur Nienhuis had just arrived. Dr. Albert Deisseroth, who is now at M.D. Anderson Hospital, had just arrived. French Anderson was a molecular hematologist who had just arrived. I had thought that I would be playing a significant role in the Intramural Program of the Institute. As it turned out, since Dr. Simon was brand new, he did not realize that there was quite a separation between the intramural and extramural programs in the Heart, Lung, and Blood Institute. My role in the Intramural Program in 1973-75 was almost as an observer. I was welcome to go to rounds, to see what was happening, but my actual responsibilities were entirely administrative—those that I was paid for and judged by—in Building 31. So I stayed there for only two years. I did not elect to stay a third year.

But during those two years I was involved in several interesting, and subsequently important, areas. As a classical hematologist I had not given

very much thought to blood transfusion. I trained as a coagulationist. I had been involved in some hemophilia studies at Johns Hopkins. When I came to NIH, two of the large programs that were being established at the Heart, Lung, and Blood Institute were in the hemophilia area, in what was then called Blood Resources, which was really blood transfusion. NIH had commissioned a study by Booze, Allen and Hamilton of blood resources in the United States in the early 1970s. Because the system of collecting, delivering, processing, and using blood in the United States was felt to be sub-optimal at best, a major effort was made by NIH, centered in the Heart and Lung Institute, to develop safe, available, cost-effective transfusion services for the United States. They established a Blood Resources Program.

In the Blood Resources Program were studies of post-transfusion hepatitis, since that was the major risk incurred in blood transfusion at that time. The figures indicated that as many as 30 percent of all subjects transfused with blood in the United States developed hepatitis in the late 1960s and early 1970s. There was a Hemophilia Program as well, which was fine for me because I had done some hemophilia studies earlier.

For the two years that I was there, two of the things that I was assigned to do involved blood resources with post-transfusion hepatitis and hemophilia. In fact I was instrumental in two of the large contracts that were let. One was a multicenter prospective study of post-transfusion hepatitis called the TTV Study, or Transfusion-Transmitted Virus Study. The second was in establishing a chimpanzee breeding colony in the United States for hepatitis research. The chimpanzee was the only animal model for post-transfusion hepatitis, and importation of chimpanzees from Africa was becoming difficult, bordering on impossible. Chimpanzees were very expensive, but even at any cost, the animals were not to be had. That was really limiting our transfusional hepatitis studies. As it turned out, both of those subsequently were key elements in the AIDS epidemic.

I stayed for two years, and at the end of 1975 I was looking for a clinical research position. I was very interested in blood transfusion services and was looking at programs around the country, one of which was a very small program here at the National Institutes of Health. I talked with Dr. Paul Holland, who had just become Director of the Program here, and he told me that there were no more positions available. One of their positions they had committed to a young man who had trained with me in medical school and had been on the house staff with me at Hopkins. He had come to NIH two years earlier. This was Dr. Peter Tomasulo. But, at the last moment, Dr. Tomasulo decided to go to a training program in Milwaukee. A position became available in the Clinical Center, in what was then the Clinical Center Blood Bank, and I took it.

Today, Dr. Tomasulo is Medical Director of the American Red Cross, so he stayed in this area. He is back in Washington and is Director of Blood Services across the country. As I said, he was a classmate and he is a close friend of mine.

So I came to the Clinical Center in 1975, to spend one year learning the hands-on laboratory aspects of blood transfusion. It was a small, but very exciting program at that time because it had probably one of the most important studies of post-transfusion hepatitis. This was something that I had been exposed to at the Heart and Lung Institute. Dr. Harvey Alter, who had spent his prior career primarily in post-transfusion hepatitis, was now here. He was the co-discoverer of the Australia antigen, which is now known to be the hepatitis B virus. He had continued prospective studies of patients in the Clinical Center who had undergone open heart surgery, collecting specimens from donors, and from the patients after transfusion for years, and freezing them away for prospective studies. Dr. Paul Holland, who was also interested in post-transfusion hepatitis, was here. He has published numerous papers primarily on the clinical aspects of post-transfusion hepatitis. Then there were several other individuals, who were among the best serologists in the country, interested in serology of blood. But the major research interest was in transfusion-transmittted disease, and in 1975 that meant hepatitis.

That is how I arrived here. Although my primary interest had been in coagulation, because of my experience at the Heart, Lung, and Blood Institute and because of the interest in post-transfusion hepatitis here, I became first peripherally, and then directly, involved in transfusion-transmitted disease.

Harden: I noticed in looking over your publications that you have many methodology papers. Have you been very interested in developing new techniques, methodologies, or instruments, in this specialty?

Klein: I have always seen myself more as a clinician, but I think it is fair to say that a number of the things I did had to do with technologic ways of managing patient care—cell separation, collection and processing of blood components. The Clinical Center was the ideal place to do that at the time, first of all because of its unusual patient population, and secondly, because of excellent engineering support in this hospital. Third, in the mid-1970s money for equipment was not nearly as scarce as it is now at NIH, and it was certainly much easier to obtain than it was at the university hospitals, for example. So you could do a number of things here yourself if you wanted to. Staff were hard to come by, but equipment was relatively easy. If you wanted to do studies of modification of existing equipment for therapeutic purposes that was doable.

Harden: You became Chief of the Department in 1983?

Klein: That is correct.

Harden: We are jumping ahead here a little. But I would like to ask one question. This was the Clinical Center Blood Bank before 1983 and then it became the Department of Transfusion Medicine. Why did the name change?

Klein: I wrote an editorial on that for JAMA in 1987 on the fiftieth anniversary of blood banks in the United States. The first blood bank in the United States and in the world was established at Cook County Hospital in Chicago in 1937. The individual who established the American Blood Bank was a clinician-pharmacologist-internist, and blood banking at that point was more or less a clinical specialty. Prior to that, if you wanted to transfuse blood you needed a surgeon, because you connected vein to vein. So, surgeons and obstetrician-gynecologists did most of the transfusion around the world.

The advent of being able to anti-coagulate and store blood meant that you could get rid of the surgeon and have a new kind of individual in charge. Initially the individual was a clinician responsible for knowing when a transfusion might be necessary, finding donors, and then putting the blood into the proper anticoagulant preservative solutions. Much research during the 1930s and 1940s was done in that area. But gradually the specialty was taken over, almost by default, by the pathologists who ran laboratories, because it seemed as if the important part of blood transfusion was cross-matching and compatibility. What was needed was to have a group of skilled technologists who would take blood from the donor and from the recipient and then find ways in the test tube of predicting their compatibility. So transfusion sciences shifted to the laboratory run by a pathologist and were taken care of by technologists and technicians.

By the 1970s and early 1980s, it seemed to me that things had shifted away from that. We were pretty good at doing the technical things and cross-matching, and that was not much of a problem. The major problems in blood transfusion were clinical problems. It was transfusion-transmitted disease; it was collecting large numbers of single donor components, possibly collecting components from a sick individual for their own use, so-called autologous transfusion. There were therapeutic procedures. To lower the white count in a leukemia patient acutely using a machine, you had to feel comfortable taking care of patients. Mostly the pathologists did not want patients in their blood bank. They would rather just draw units of blood from healthy people and then test them in the laboratory.

It seemed to me that blood transfusion was becoming more of a clinical discipline again. It was shifting back. That is why I wrote the editorial and used the phrase “transfusion medicine.” I did not originate the

phrase—it comes from the German—but this was the first Department of Transfusion Medicine in the world. We felt that departments of transfusion medicine would have a blood bank—they would not be a blood bank, they would be more than that—they would preserve, cross-match, test blood for compatibility, but they would also be clinical consultants for the use and collection of blood, and for therapeutic treatments with all kinds of blood components. That was the reason for the name change. It was very well thought out.

I can remember when the name for this department was generated. I was sitting at lunch in the NIH Cafeteria with Dr. Joel Solomon who, at the time, was on detail here. He was detailed from the FDA (Food and Drug Administration). Dr. Harvey Alter was also there. I think there were the three of us. There might have been one more person. Unfortunately, I do not remember. We were tossing around names that might better reflect the mission of the department.

"Transfusiology" had been suggested—the Russians used a similar word—and that seemed somewhat pretentious and difficult to get out. After a number of different ideas, Transfusion Medicine seemed to fit the bill, and so we changed the name.

Harden: I am very glad to know that story. Dennis, do you have anything else you wanted to ask about the pre-AIDS period?

Rodrigues: I am interested in the TTV, and the chimp breeding colony. But I imagine when we start talking about AIDS you will tell us more about these.

Klein: I will. Actually, again, I can remember exactly when the name TTV was generated. It was at a meeting of contractors and contractees—I guess I was the contractor since I was with the Institute—in Los Angeles, California. Dr. James Moseley, who was an epidemiologist concentrating on hepatitis, had gotten the multicenter contract. When we were trying to determine what to call it, as the contract was for post-transfusion hepatitis, Jim said, "There are probably a lot of other viruses, certainly a lot of other viruses. Let's call it the 'Transfusion-Transmitted Virus Study' instead of the 'Post-Transfusion Hepatitis Study.'" Of course, AIDS was not even in anyone's mind then, but cytomegalovirus was being thought of, and we were certain that there were other viruses that were transmitted by blood.

Part of that study was to freeze away specimens for posterity, and a big part of the contract was, in fact, the freezing facility for keeping those specimens from donated blood and from patients who had been subsequently tested. Those specimens are still available, by the way, so if you want to go back to the 1973-1980 period and find out if an agent was in the U.S. blood supply, you can still pull some matched sera, and see if a donor and a recipient had the virus—if the recipient was negative prior to

the transfusion and the donor was positive and then the recipient became positive after the transfusion—because those specimens are still frozen.

Harden: That is quite a resource.

Klein: It was an enormous resource, and it was an enormous battle, as you might imagine, to get the money to do that study. The only reason that we could do it, I think, is that at the time the hepatitis rates were in the range—no one was really sure, and that is why it was a prospective study—but they were felt to be in the range of 20 to 30 percent. Today, with hepatitis rates probably below 2 percent, a proposal to fund a prospective post-transfusion study was discontinued about two years ago. Everyone had submitted proposals but the money was not there because it looked as if it was not a big enough national problem to merit the several million dollars that it would have cost to run the study.

Harden: We should actually do a whole interview about the Clinical Center's involvement in hepatitis.

Klein: But that is another day?

Harden: Yes, but let us try to get to the beginning of AIDS. Can you recall when you first became aware of a problem? Some people heard others talk about it at hematology meetings in 1979 and 1980. Other people were not aware of it until 1982 or so. When did you first become aware of AIDS?

Klein: I had not heard of it at hematology meetings at all. In fact, I think I first became aware of AIDS in 1981 when Dr. Clifford Lane who was a Clinical Associate in NIAID at the time, began to bring in some unusual patients with curious immunologic deficits for study under one of Dr. Anthony (Tony) Fauci's protocols. It was not called AIDS at the time. It was a rare disease. It had cellular and humoral immunity defects. Since Cliff and Tony were interested in these defects, they were importing patients from San Francisco, Chicago, and Los Angeles, places that eventually became the hot spots for AIDS.

I remember specifically—and I think this was either in late 1981 or early 1982—that Cliff came down and he wanted us to collect some white cells from these patients. We had the instruments to do it, so we could collect concentrates of white cells for laboratory research from these patients, many of whom had relatively low white blood cell counts. But we could put them on an instrument for a couple of hours and collect large numbers of cells.

Harden: Could you give me more details. Did you go to the patients' hospital rooms, or did they come down here?

Klein: No. They came down here.

Harden: Just like the donors?

Klein: Like the donors, but we had a separate area for patients. We tried to keep our patients and donors separated. I can remember when we saw these patients, of course, nobody knew what kind of disease they had, or how it was acquired. It appeared to be acquired—because the people we were seeing were adults—but how it was acquired was simply not known. An infectious etiology was certainly a possibility, and we were thinking about this possibility at the time, although it was not by any means at the top of the list. I know many people knew it all along, as I hear now in 1992 and 1993, but we did not. On the other hand, we took great precautions with our staff.

Harden: I would like you to talk about that too.

Klein: Yes. Our staff did not wear masks, but they were all gowned and gloved, which was very unusual at the time. It was not just for those patients, but also for some of the other unusual patients we saw in the Clinical Center when we were not exactly sure what they had.

By, I guess it was, late 1982 or early 1983, when the name AIDS was coined, I can also remember giving Dr. Ed (Edward) Rall a tour of our facilities. Ed was a very loyal blood donor, by the way, among other things. We were giving him a tour, and he walked through the clinic that we had on the D Corridor. At the time we were getting blood from one of these patients, and Ed said, "Be very careful about these patients."

Harden: On whom did the responsibility fall to decide what precautions the staff would take?

Klein: That was my responsibility at the time. We sat down and we talked to the staff about potential risk. I must say probably more likely than I would a year later than that, because I, honestly, in my own mind, was not convinced that this was a transmissible disease. I did not know. I felt we ought to be cautions, and so we gowned and gloved.

Harden: Was that the standard procedure for hepatitis?

Klein: If you knew someone had hepatitis, in other areas of the hospital you were never gowned. But we gowned because with our instruments we could break seals, we could spray plasma or blood, or, since we were carrying large volumes of materials in plastic bags, if we dropped them which happened one time, we could get it all over the place. We insisted that individuals wear gowns, as well as gloves, and we always did that for the hepatitis patients too.

Harden: That is very interesting. Let us go back to when you were working with Dr. Lane, taking white cells from his patients.

Klein: Within the next year—it was either in late 1982 or possibly early 1983—I think the name of AIDS had been coined by then—we knew that these patients were severely immunodeficient in both arms of the immune system. Drs. Lane and Fauci came up with an interesting strategy. They wanted to know whether they could reconstitute the immune system of these patients, and, if so, how they might do it. Probably the easiest way, if you could do it, would be to find identical twins, one of whom was infected and the other of whom was not infected, and do a bone marrow transplant. By this means, you could maybe transfer immune cells from the uninfected identical twin to the infected one.

Cliff came down and asked if we could help. He had lined up the NCI (National Cancer Institute) people who were doing bone marrow transplants and that was no problem. He asked whether we could help with reconstitution of immune cells. I said, "Yes, we could do that. What we could do is use our cell separating technology to collect large numbers of lymphocytes from the healthy twin, and then you could reinfuse them into the infected twin." Actually this had been done in another instance at NIH years earlier, before I was here, in only one case that I know of. It was a case of a child with an inherited severe combined immune deficiency. A fellow by the name of Fitzpatrick, who was an immunologist here, along with an NCI investigator by the name of Dr. Jay Freireich, had collected large numbers of normal lymphocytes to give to a young girl who had a systemic fungal infection and severe skin disease. She had gotten transient immune reconstitution.

So, I became an associate investigator on that protocol, and Cliff, I am sure, has the original protocol that we used. We got multiple sets of twins and did, in fact, demonstrate that you could reconstitute these individuals using bone marrow transplants and multiple collections of lymphocytes—immune white blood cells—from the healthy individual and putting them back into the infected individual. However, once you started doing this, they reverted to their former situation within a matter of months. We published this in the *New England Journal of Medicine.*

One thing that this research did suggest to us, again, with other evidence mounting, was that this was probably an infectious process, and that we had not got rid of the agent. No matter what you did to reconstitute the immune system, unless you get rid of the agent from the patient you were not going to cure the patient. This subsequently resulted in a variety of modified protocols continuing actually up to the present time, where the patient is treated with a variety of drugs plus cells from the identical twin. Cliff would be able to tell you how many there have been. I think they

have had thirty sets of identical twins, one of whom is infected and the other of whom is not. If you had asked me back in 1982 would there be that many, I would have said, "This is insane. This will be a study of two or three sets of twins, if we are lucky." But in point of fact, Cliff has had an enormous number of twins who have been involved in these studies, right up until the present time where we are now growing the healthy twin's cells, expanding them in incubators, and giving them back to the infected twin. The next step may be gene modification of those cells. So, we have moved from a sort of crude clinical science to very sophisticated science, immune reconstitution of these patients using our identical twin adoptive immunotherapy.

Harden: Was the FACS machine (fluorescent-activated cell sorter) used to sort out the white cells from these healthy twins? Did you use something else?

Klein: We used the cell separator, but they may have used the FACS to analyze what kind of cells these were, and then what happened to them after they were transfused and over time. But actually to collect this volume of cells, and we are now talking about perhaps 10^{10} white blood cells—that is an enormous number of cells—the only way you can do that is with the automated equipment that we had had originally designed to collect transfusable components, such as platelets.

Harden: This takes up back then to what you were talking about before we started the interview, about the platelet separation.

Klein: That is right.

Harden: Perhaps I should ask you to talk about that at this point—and to bring it up to AIDS.

Klein: I just wanted to mention that this particular blood bank (at the NIH) was one of the first to start collecting platelets by platelet pheresis. That antedates my arrival here. It was done by manual platelet pheresis, in which there was a series of multiple plastic bags. You collected a unit of whole blood from the donor, spun it down, separated out the platelets, gave the donor back the red cells and plasma and drew a second unit. Over a period of four hours or so you could get the equivalent of four platelet concentrates from four units of blood drawn sequentially from the donor.

When automated devices became commercially available, we were also one of the first institutions to switch to collecting platelets exclusively with automated devices. By using what is essentially a clinical centrifuge to which the patient's vein is attached, you can, on-line, at the same time, collect six to eight units of platelets processed from a single blood donor and give every other blood component back to the donor.

By way, again, of history, one of the first instruments, the so-called NCI-IBM blood cell separator, was invented at NIH by Dr. Freireich and an investigator from the IBM Company, so we felt comfortable with this kind of equipment. In fact, some of the nurses who were instrumental in those first studies—for instance, Regina Dowling, who was one of Dr. Freireich's nurses—worked here for me doing platelet pheresis subsequently. So, we felt comfortable with that. We were using the equipment to collect platelets for transfusion purposes. Then, since we had the instruments available, we were using them to collect a variety of different cells, or plasma, for researchers at NIH. It was very natural to use these for some of the AIDS studies.

Harden: It seems that it was right after we began to understand about the cellular immune system, what a T cell is, what a B cell is, that this disease appears that strikes these components. In looking at it from a hematologist's point of view, what could you have done if AIDS had struck in 1955?

Klein: I think it would have been a disaster. First of all, one of the other very important discoveries was IL-2 (interleukin-2) or T-cell growth factor, and one of the very important investigators in developing that growth factor was Dr. Robert (Bob) Gallo here on campus. What you probably do not know is that one of the ways he could investigate this was by getting buffy coats that were prepared in the Blood Bank. We removed the white cells from donated units of blood because these small numbers of white cells did not do the patient any good—in fact, they sometimes caused fevers in the patient—and we could easily spin them off. So we would spin them off and instead of discarding them we would offer them to investigators. We never advertised it because the response would be overwhelming. But word of mouth was our best advertising, and Gallo's laboratory was a large user of these cells. That was a resource that was not available to many other people, so it made (possible) discovery of the ability to grow retroviruses in the laboratory. That was an important contribution.

In the 1950s we could not have done that. We could not have grown these viruses, for one thing, so we really would have been out of luck. As you said, in the 1950s we did not quite know what the lymphocyte did, and we certainly did not know about all the different kinds of lymphocytes and their different functions and roles. I think AIDS would have devastated the population. I am not sure what one would have done with this disease. We did not have any of the tools to deal with it in the 1950s or 1960s.

Rodrigues: I was curious. You talked about the earlier attempt to transfuse cells from identical twins with the child who had severe combined immune deficiency disease. Did it work in that particular case?

Klein: You might have to call Dr. Charles Kirkpatrick. The last time I heard, he

was in Denver. But I found an abstract. The case was never totally written up in full form. It was only an abstract presented at the Infectious Diseases (Society) meetings saying that the transfusion did work in terms of helping to clear the fungal infection and reconstituting this patient.

For a patient who has an inherited abnormality, it should have been a very dangerous thing to do. If you take lymphocytes from someone else and put them in a person, you should get graft-versus-host disease. Maybe they did. I do not know. It certainly did not say in the abstract. I hope they did not. Or perhaps they did not because the child was not so immunosuppressed that that was an issue. But that may have been one of the concerns. I simply do not know why no one else was doing that, or why there was no follow-up of this patient, or why it was never published in full form. I dug that case up and it was one of the things that interested me. But by the 1970s we could deal with that, because we could irradiate the cells. We did not have to worry about graft-versus-host disease in identical twins. We could go ahead and reconstitute people if we wanted to without that particular risk. So, I think that that worked, but I do not know if there were side effects or adverse effects.

Harden: You were beginning to see and to collaborate with people on these early AIDS patients, at the end of 1982, and the beginning of 1983. In 1983 you become Director here, and it was also late 1982, early 1983, if my memory is correct, when it dawned on people that the epidemiology was showing bloodborne transmission of AIDS. You had a big meeting in Atlanta in January 1983, and the DHHS (Department of Health and Human Services) Secretary assigned NHLBI (National Heart, Lung, and Blood Institute) to be the lead institute with regard to research on AIDS and blood transfusion. What do you recall about this period?

Klein: Before that several things happened. There was a report from the CDC (Centers for Disease Control), and also by word of mouth, of a case of a baby in California, who was infected by a unit of platelets that eventually was traced back to a man who died from AIDS. The so-called Ammann case, was reported, I think, in December of 1982 in the CDC's *MMWR* and subsequently, in April of 1983, in the *Lancet*. This was a case that I heard talked about of transfusion-transmitted AIDS in a baby. That was subsequently published in April 1983 in the *Lancet*. But this was being talked about in late 1982.

Then there was the hemophilia story. Having been associated with hemophilia at Hopkins—for a year, I took care of 100 hemophiliacs, the largest number of hemophiliacs in the State of Maryland—and when I was at NHLBI, I had been in charge of the Hemophilia Program, so I had been aware of the tremendous hepatitis problem. At that time, the second leading cause of death in hemophilia was liver disease. The first was bleeding. Our goal as to make more concentrate available, to get

hemophiliacs to be able to transfuse themselves at home, because they were dying of bleeding. But I retained an interest in hemophilia. In fact, one of the families that I had taken care of at Johns Hopkins subsequently came to NIH and was being treated by Dr. Ray Shulman. They picked up their concentrate from me in the Blood Bank. So I had kept an eye on the hemophilia story, even though NIH was not doing much, almost nothing intramurally on hemophilia. Ray Shulman was doing a little in the late 1970s, and early 1980s.

But suddenly the hemophiliacs started to be reported, first, with this unusual *Pneumocystis* pneumonia, and second, when people started to look at them, they found the inverted helper/suppressor ratio. Now, along with the gay men that had been reported, people were starting to talk about hemophiliacs, and there was a case or two associated with blood. I must say in all honesty that in 1982 I was suspicious because of the post-transfusion hepatitis story, because of hepatitis in hemophiliacs, but I was not convinced that this was a transfusion-transmitted disease, not by a long shot. Who can say much about a baby? That baby might have had an inherited immune deficiency syndrome of some kind and become awfully sick and died. Certainly the baby got one unit of platelets from someone who died of AIDS but, after all, there were about eighteen million units of blood components transfused in the United States every year, and 12 million units of red cells. If AIDS was transfusion-transmitted—according to our thinking in 1981-82—and it was like hepatitis, we should have been seeing a lot more of it, and we were not.

Hemophiliacs are an early warning system. Many people have said, "You should have known back then (that blood transmitted AIDS)." But in fact, when I was with the Heart, Lung, and Blood Institute from 1973 to 1975, we were aware that there was some suggestion that blood transfusion caused immunosuppression, long before AIDS. In fact, we let contracts to look at the immune system of hemophiliacs. So it did not surprise me that hemophiliacs would become immune suppressed, and it did not necessarily say to me, "This is the AIDS agent, or the AIDS virus."

Harden: I have one other question along those lines. What is the incubation period for hepatitis B?

Klein: From the time of infection to the time of clinical disease, maybe six weeks to six months.

Harden: Okay. So with AIDS you are dealing with an entirely different incubation period—this is hindsight again.

Klein: We also knew that you could transmit cytomegalovirus and, under unusual circumstances, you could transmit hepatitis A (through blood products). You can transmit malaria, a variety of other parasites, and bacteria, but all

of this was within a matter of days to months. Nothing else was years in transmission that we knew of. To think that there could be such a long period of time before there was any suggestion—and remember we did not have a test—of a clinical disease was difficult to accept. Certainly, in my own mind, it was not proved in 1982, not by a long shot. I know about the meeting. I was not an attendee, but I know about the meeting in January of 1983. I have subsequently seen much of the data from that meeting.

Dr. Bruce Evatt, who was one of the leading investigators at the CDC at that time, was actually a year ahead of me in the Hematology Department at Hopkins, and a close friend. I can remember arguing with him at Dr. Conley's house, when Dr. Conley had a gathering of his former fellows—I wish I could remember the date, but we can find it out because it was the date of the Osler Symposium at Johns Hopkins—and many of the former fellows came back and Conley had them over to his home. I can remember sitting and arguing with Bruce that AIDS was not proved to be a transfusion-transmitted disease, even though the evidence was awfully suspicious. He had more data than I did, and the lesson there is never argue with someone who has more data than you have. He had the epidemiology from the entire United States at the CDC. So, he felt strongly that it was a transfusion-transmitted disease. I was skeptical, but it smelled a lot like hepatitis, and so I was suspicious.

But I remember what some of the other arguments were. In hepatitis we used to see transmission in institutions. The famous studies were done at Willowbrook, in New York, where they actually gave hepatitis to children, and they justified this by claiming that most of these kids would be infected with hepatitis B anyway from being in an institution. I thought that you ought to be seeing this disease (AIDS) in institutions, and we were not.

Also, there was the issue of needlesticks. There was about a 15 to 30 percent risk of hepatitis B if you were stuck with a known positive needle. Why were we not seeing health care workers, who are stuck with needles all the time, with AIDS? Surgeons? Why were we not seeing dentists? They should be getting AIDS out of proportion to the general population. That was actually looked at, and it appeared that they were not. They did not have a significantly higher number of cases than the general population. So, there were arguments that one could make that this did not look like a transfusion-transmitted, or blood-transmitted disease. Then, there was the data on the other side, which obviously began to mount up. I always mark my own absolute conviction from the publication that the CDC had in the *New England Journal of Medicine*, (Dr. James) Jim Curran's publication, on transfusion-transmitted AIDS, which was in January of 1984. I had heard of that manuscript and talked about some of the data before that, so my conviction was actually slightly before the publication date, but it was not in 1982 or early 1983.

Harden: But by the date of that publication you were convinced that there was some sort of agent, even though it had an unusual incubation period and was different, and that it was something new?

Klein: That is right. I thought it was probably a virus.

Harden: At that point?

Klein: At that point.

Harden: A virus we did not know anything about?

Klein: That is right. Do not forget, we had not seen a new virus in the blood supply in thirty years, and retroviruses did not cause human disease, we thought, with the possible exception of T-cell leukemia. So these were all disturbingly new concepts. A disease with an incubation period of ten years, or seven years at the time, whatever was believed. A retrovirus. A disease that was transmitted by blood, but was not seen in these other situations. I think it was hard to be convinced earlier than early 1984. Good luck to the people who were absolutely convinced earlier than that. There were some who fervently believed it was transmitted. One of the regional public health officers fervently believed it, but he thought it was the hepatitis B virus that was causing it. Many people who had many theories were only partially right. I think the officer was as wrong as the people who did not think it was caused by a virus, because hepatitis B did not have anything to do with it.

I can tell you that since we were able to collect biologic materials from these patients, a number of very well-respected scientists at NIH came down to talk to me about the work that they were doing for which they would like to get biologic materials, if we could help them, and the theories which I thought were very plausible had nothing to do with infectious disease. It was immune suppression from antigens on spermatozoa crossing the mucosal barrier in the rectum. All kinds of theories that today appear ludicrous, but, in 1982 and 1983, appeared very plausible.

Harden: One of the great critiques of the AIDS activist groups and the publications that have come out is that Government scientists did not pursue this research as vigorously as they might have because they were homophobic. Did you see any of that in the Clinical Center, and could you characterize the patients, or the interaction between patients and physicians?

Klein: As far as I am concerned, that is absolutely wrong. First of all, by the time we realized that there were more than three or four cases in the United States—this may sound cold—and that scientifically these were very

interesting cases, people were rushing to study this disease in the Intramural Program. It was going to make for publications and fame, which I think, without any question, is what drives many of the scientists at NIH.

One of the first patients here was actually a woman from Chicago, but, as you might guess, the large majority of patients were gay men. I never saw any indication that people were reluctant to study these men because they were homophobic. Perhaps that existed somewhere in the Intramural Program, but not here. It never crossed the mind of anyone I talked with. But then the people in my circle—Cliff (Lane) and (Tony) Fauci, Dr. Henry Masur, and Dr. Harvey Alter—became very interested in this disease, because it smelled a lot like hepatitis. Alter did the first studies in chimpanzees along with Henry Masur. No, I never saw that attitude. If we could have gotten more patients, more money, and more resources, we would have done more. But again, this was a fairly unusual disease compared to cancer, let us say.

Rodrigues: In the chronology of things, at the time when you were convinced that this was a viral-borne disease and there was still an absence of any test, another one of your immediate concerns might have been the problems that your department was going to have in attempting to ensure the safety of the blood that was being used in the Clinical Center. Could you talk a little about that problem, and what thoughts people had on other types of surrogate markers that could possibly be used as indicators?

Klein: First, let me go back a bit. This may be of some interest to you. Bob Gallo wrote a letter to the *New England Journal of Medicine* in 1982, I think—it might have been early 1983—indicating that he had found a retrovirus in buffy coats from the NIH Clinical Center Blood Bank. This caused an uproar. Dr. Paul Holland, who was the Chief of the Blood Bank at the time, almost got into a fist fight with Gallo. Betty Colbert may have some letters about this that she can give you. Paul, first of all, said that Gallo, in his publication, suggested that the Blood Bank was working collaboratively with him, which we were not, and that we endorsed his letter, which we did not. We were not signatories.

The second thing Paul Holland said was that Gallo's publication might inflame the concern about blood transfusion because it might suggest that these retroviruses would be deleterious to human beings and there was not a shred of proof that they were. Finally, the buffy coats that we had given out to Gallo and to everyone else were strictly for research purposes. Trying to find the donors who had given these in order to study them was simply not cricket. Of course, it was not, and is not. One of the donors—I think this was HTLV-I that Gallo found actually, not HTLV-III—but it raised the issue of retroviruses going into human beings and causing

disease. One of the buffy coats actually came from a Japanese researcher who was back in Japan and HTLV-I is endemic in Southwest Japan.

But that was a little footnote to the blood problem, because we were all very sensitive at that point about whether or not AIDS was being transmitted from an agent that went through blood. In fact, the meeting at the CDC in January of 1983 was the first big meeting to try and address what looked as though it was going to be a major issue. I am not going to say a major public health threat, because I think most of the scientists, did not think it was, or were not sure. But in fairness, several of the epidemiologists at the CDC, including Dr. Donald Francis, probably Bruce Evatt, I think, and several others, felt that there was enough data that something needed to be done. The scientists from NIH—Dr. Amoz Chernoff was the one from NHLBI, and Dr. Kenneth (Ken) Sell—I think were sort of neutral. Then there were some blood bankers who were concerned about the issue of being able to supply enough blood to the United States. Supply was always an issue. A large concern was that if you put in any kind of screening device that took out large numbers of donors without pretty good proof that you were helping the blood supply, you might, in fact, end up with people dying because there was not enough blood available.

Amongst the kinds of indicators that were suggested at the time, the first were surrogate tests. The CDC had a list of a dozen or so surrogate tests that might be beneficial. Actually, we had begun using a surrogate test for hepatitis in 1981. We were the first blood center in the United States to use a surrogate test for hepatitis by about four to five years, and we were roundly criticized for doing it. We did it because our population studies by Harvey Alter demonstrated that we could cut down on post-transfusion hepatitis by about a third in our population in the Clinical Center, and so we felt obligated, based on those data, to do that.

The TTV Study subsequently showed that the same surrogate test was effective in the multicenter study. Surrogate tests were therefore nothing new for us, and we put them in very early for hepatitis.

None of us had seen the data presented by the CDC. That was a closed meeting. In fact, the sheets and graphs that were passed out were collected before the end of the meeting, so they were not widely available. I have seen them subsequently, and I can tell you that I would not have introduced one of those surrogate tests based on the data that they had. So I do not criticize those people who said, “What you are going to do is eliminate an awful lot of normal individuals and threaten the availability of the blood supply while you are not going to improve its safety.” I think that that, based on what I know now, was a reasonable criticism.

On the other hand, some things were becoming clear. One seemed to be that gay men with numerous sexual contracts were a risk. We knew that already from hepatitis and we probably should have been thinking about getting heterosexuals with multiple sexual contacts as well as gay men out of the blood donor supply, but the transfusion community had not done that. At that point is seemed that if there was a clear association, we ought to do that.

There was an issue about Haitians. The disease seemed somehow to be endemic in Haiti for whatever reason. Let us then prohibit Haitians from being blood donors. That would not have eliminated many American blood donors. It might have done some good. Again, it did not seem an unreasonable thing to do, even if you alienated some people who were born in Haiti.

Hemophiliacs seemed like a risk group. Later we defined this as risk behavior. Hemophiliacs were not really donating blood anyway, but we put them down as well.

Drug users were another group that were now being looked at. We had always kept them out of the donor group. If a person used intravenous drugs he or she was not allowed to donate blood. But we would emphasize that.

And then we said sexual contacts of any of those people.

It was the four H's: the hemophiliacs, the homosexuals, the Haitians, and the heroin addicts, and their sexual contacts. The American Association of Blood Banks, the Council of Community Blood Centers, and the American Red Cross, the three major collectors in the United States, put out a joint statement saying that we should try and eliminate these individuals from donating blood.

Harden: What date was this?

Klein: I think they framed the statement in January of 1983. It might have come out then, but I believe it came out in March of 1983.

Harden: I know there was a meeting in Washington, two days, I believe, after the Atlanta meeting.

Klein: Yes. I was not a party to that.

Harden: But then DHHS Secretary (Margaret) Heckler, did something in March?

Klein: That is correct. A statement came out over Dr. Edward Brandt's signature, I think. Heckler had a news conference and I have actually seen the

transcript of it. She had a news conference, and Brandt put out a Public Health Service position. The position was essentially the same position as the joint statement.

The other thing we thought reasonable to do, as we now knew some of the signs and symptoms of AIDS—night sweats, unexplained fevers, unexplained diarrhea, shortness of breath, white spots in the mouth, candidiasis, thrush, Kaposi's sarcoma—was to decide, "We will ask the blood donors these questions as well. If anyone says they have any of these conditions we will exclude them." We did no some things but they were historical kinds of things and that we thought might not improve safety, but possibly might, and would not disrupt the system and therefore limit supply.

As it turns out, asking the questions about signs and symptoms probably did nothing because people with AIDS do not come in to donate blood. By that time in their disease they are not blood donors. The questions about risk behaviors clearly were important and remain so to this day.

Harden: Is that when you made up your first form with those questions on it for the blood donors at NIH?

Klein: Yes.

Harden: I picked one up for the museum collection in 1987 or 1988.

Klein: We had a form in 1983. That was not the earliest form, but I am not sure that we would have had access to the earliest one. This one has the donor's name on it. We would have to get rid of that.

Harden: You do not have to find it now. I just wondered.

Klein: We started asking in 1983 with a special form, because it takes time to print cards. Especially in the government it takes a lot of time to print cards. We did not actually redo our donor card until October or November of 1983, but clearly by April of 1983, and I think earlier than that, we were asking questions by giving donors a different printed sheet. On the donor card all we had in one of our blank spaces was something to the effect that these questions had been asked. The screening nurse had to check off that she had asked the donor these questions, but the questions themselves were not on the donor card until October or November 1983. They were on a different sheet. That was our approach to questioning the donors.

Harden: Maybe we can eventually try to get the earlier card, and then the series, to put in the archives.

Klein: Sure.

Harden: That would be very good to have.

Klein: We were very concerned about the transmission of AIDS. We thought that there could have been a transmissible agent, but we were not concerned enough that we considered using surrogate tests which, by mid-1983, were being talked about but had not been published anywhere. In fact, the manuscript that came out of that January 1983 CDC meeting was rejected by the *New England Journal of Medicine.* I do not know why it was rejected. I was not one of the reviewers. But it was submitted to the *New England Journal* and rejected, I think in early 1984, and not in 1983. No one was using surrogate tests for AIDS, or HIV, or anything else that was associated with AIDS. No one ever did in the United States, with the exception of a few California blood banks who were doing it, so they say, one for a research protocol….

Harden: Was that the person at Stanford?

Klein: Stanford. Dr. Edgar Engleman was doing helper/suppressor ratios. Subsequent to that, Irwin Memorial Blood Bank was using core antibody tests which were later shown to correlate reasonably well in studies we did here at NIH actually with anti-HIV, or anti-HTLV-III, as it was then called. Then a couple of other California blood banks, one of which was a Red Cross blood bank, asked permission of the Red Cross to do this on an experimental basis to try and get some data. But there was a lot of pressure in California because there was real panic in the San Francisco area. In the Washington area, not only was there not panic, there wasn't general acceptance that this was a transfusion-transmitted disease.

Rodrigues: You mentioned AIDS has some perhaps some beneficial effects on certain clinical practices. Could you say a little bit about the overall impact of AIDS on other aspects of transfusions.

Klein: Yes. It was always very hard to convince clinicians that too much blood might be bad. In fact, I had a very prominent Boston physician, son of a Nobel prize winner, who told me he did not see post-transfusion hepatitis in Boston. In fact, if these people were infected six weeks to six months after the transfusion, and the original illness was relatively mild, they might not have reported it to their physician. So that information wouldn't have gotten back to the blood bank. Or, they might have reported it to their physicians, who said well, it is a mild case of hepatitis, and might never have reported it to the blood bank. So the point was, he probably wasn't seeing it, but it was there. So, people were using a lot of blood, a lot of times for the wrong reasons, a lot of times unnecessarily. Patients didn't know the difference, there was no consumer advocacy. Patients didn't say, "Wait a minute, don't transfuse me until I really need it."

Patients weren't saying anything. They felt if your doctor felt you needed blood, you got blood.

Harden: In the 1982-83 period, what would you have said to a family member or friend who needed surgery and was anticipating a transfusion?

Klein: I was attending on the service here, so I saw lots of people who required transfusions. And I always told them the risk of hepatitis was substantial—at that time, I believe it was about 10 percent—and I felt that that was substantial, although most of these cases these cases did not develop severe effects. Studies done in this hospital suggested that maybe half of the cases went on to have chronic liver disease, and so that was always the number one concern.

Then I said, "There are a variety of other illnesses that you might get, and most of these are relatively uncommon or relatively unimportant."

Harden: But you did not see AIDS as a major threat at that time?

Klein: Not in 1982. In 1982 I can tell you unequivocally that I would not have mentioned it. By mid-1983 clearly I was mentioning that AIDS might be transmitted by blood, but that it was a very rare event. I am one of those people who has been castigated ever since for saying "You are probably more likely to be struck by lightning, than you are to have a transfusion-transmitted case of AIDS. We simply don't see it." Again, bear in mind that at that period of time there were approximately twelve million units of red blood cells, or whole blood, and another six million units of platelets and plasma being transfused in the United States to some four million people every single year. If you saw twenty cases of AIDS in the United States associated with blood transfusion, they might have had other risk factors but had been transfused anyway.

Many people—four and a half million people—were being transfused, so some of those were gay males, some of them were drug users, some had been born in Haiti or had had sexual contact with Haitians. You could not really say that this was a bloodborne disease, and, if you believed it was, then you still had to say it was not very common. Even if I was only seeing half, or even if I as only seeing one out of ten cases, it was not very common. That is what I was saying in mid-1983. I was saying the risk from blood transfusion was hepatitis, and a person should not get blood if he or she did not need it. But yes, it was conceivable that AIDS was a disease transmitted by blood—very unlikely—but if it was transmitted by blood, it was probably not very common.

Harden: Okay. I interrupted you when you were describing the positive impact of AIDS on transfusion.

Klein: If you look at blood collections in the 1970s and 1980s, you see that they go up about eight percent per year. There were never good data on transfusion, but you can estimate that transfusions were continuing to climb during that period as well, maybe not a percent a year, but all of that blood was not being outdated; it was probably going into human beings. That is why more and more was being collected.

By around 1983-1984, the collections flattened out and, in fact, went down, and now they have flattened out again. The reason is that physicians are transfusing blood much more consciously, really looking for indications it is needed. I would like to think that this was because physicians have become better educated and smarter, but my own feeling, based on no data, is that it was because patients were beginning to ask questions. They were beginning to say, "Is there a risk in this stuff? What is the risk? Will I really need the blood?" And there were lawsuits. There is nothing that the transfusing physician pays more attention to than his legal colleagues or then, in all fairness, his patient who starts to ask questions and brings the issue to a level of consciousness. The patient says, "You shouldn't transfuse me unless I really need it. I'm scared. Unless I really need the blood, don't transfuse me."

So we were beginning to see a much more rational use of blood and blood components. We were beginning to have people say, "Maybe there is something to limiting exposure to donors? Maybe we should think in terms of not exposing people to 1,000 donors if we could expose them to five donors?" You started to see single donor platelet, platelet pheresis, become more prominent. I think that is a safer component for a variety of reasons.

In the mid-1980s you began to see cryoprecipitate that had been collected by blood banks from, say, 16 to 20 donors, being used for hemophilia, or being used for bleeding problems where Factor VIII was an issue, rather than the commercial concentrates which had tens of thousands of donors in the pool. By the mid- or late-1980s, these concentrates were sterilized. So the risk decreased, but at that point in time, the number of donor exposures became a real issue, and physicians tried to limit donor exposures and use less blood. If there is a silver lining to the black cloud of AIDS in the transfusion community, that is probably it.

In addition, many of the history-taking measures that were put in place to limit the risk of AIDS—the questioning about gay activity, and it got to the point very quickly, as it is today, that any male who had sexual contact with any other male since 1977 was not allowed to donate blood—all of those high-risk behavior questions, which are now asked directly of our blood donors, not only limited the risk of HIV and AIDS but clearly were instrumental in decreasing the risk of post-transfusion hepatitis. There is no question about it.

Harden: We have covered the most intense part of the crisis in terms of addressing the ideas of bloodborne transmission and protecting the blood supply. What we have seen in a number of ways is that once a virus is identified the whole process becomes much more rational, that is, when there is something to look at, people focus their studies. Could you comment on how that changed your situation?

Klein: First, I probably should mention that what I believe was the first chimpanzee study was also done at NIH. Again, we had established the chimpanzee breeding colony from the Heart, Lung, and Blood Institute back in the 1970s, and the chimpanzees were available for hepatitis research. When this disease called AIDS came along, it seemed like this might be a way to try to determine whether it was transmitted by blood. The idea, I think, was generated initially by Drs. Harvey Alter and Henry Masur.

What they did, eventually with other collaborators, was to collect components from hospitalized patients in the Clinical Center who had AIDS, or what we called ARC (AIDS-related complex) at the time, pre-AIDS. We did not know if they were infectious, or when the infectious period would be. Maybe it was before they got the disease. So, if you just took components from the diseased patients maybe you would miss it and you would not be able to transmit the disease, even though it was transmissible. We also did not know whether the agent was in plasma, or whether it was in cells, or since it was in hemophiliacs, maybe you needed protein concentrates. Maybe you also needed some other factors along with the blood. We really did not know. What Drs. Alter and Masur came up with was to take components from patients in the hospital at different stages of disease. We collected these by apheresis and we made cryoprecipitate concentrates of Factor VIII. We used white cells and plasma. We put together different blood components from different patients at different stages of disease, and then put the result into chimpanzees that were in the colony.

As there was no test for AIDS, the idea was to see: (a) did the chimpanzees get any kind of clinical disease? And then (b) were there surrogate markers, for example, changes in the T helper/suppresser ratio? Was there a decline in helper cells? Those studies were started, I believe, in early 1983.

One of those chimpanzees, luckily for us at the time, developed a clinical syndrome that had never been seen before by the veterinarians—enormously large lymph nodes with were biopsied and were non-specific. The other chimps, I think there were two or three others—and this was published in the *Lancet*—developed nothing at all. Over a couple of weeks the lymph nodes in the chimp that had become symptomatic went

back to normal anyway. None of the chimps got sick. As they were being followed sequentially, their helper cells did go down. By their being followed sequentially into 1984—by that time anti-HTLV-III was discovered—one of the workers in Gallo's laboratory developed an assay that could be used for chimpanzees. We assayed the chimps which we already thought had been infected with an AIDS agent, and, in fact, they were positive. So were the specimens that had gone into them. The paper that came out showed the clinical syndrome, the reversal of the helper/suppresser ratio, the lowered helper cells and the positive test, although we really knew before the test that something from human beings had been transmitted to animals. That was the first demonstration, I believe, in an animal model that AIDS was a blood-transmitted disease, or that it was a blood-transmitted agent that caused the same immunologic changes in a candidate model as it had in human beings.

The advent of an assay meant that you could now look at donors and look at recipients. In fact, one of the first things that happened when an experimental assay became available was that Harvey Alter went to this freezer and pulled out his post-transfusion hepatitis specimens. He had one of his fellows from Spain, Dr. Juan Esteban, who was here on a Fulbright Fellowship, go through all of them. He found two positive donors confirmed by Western blotting procedures. He looked at the recipients, and these recipients turned positive several weeks to several months after they received the blood. They had been negative prior to transfusion. Those studies, which again were published in the *Lancet*, defined the window period before positivity for antibody. It was defined from these freezer studies of post-transfusion hepatitis.

Harden: You have now raised another key question. There is a window of time before an infected person tests positive, and the blood supply is therefore not 100 percent safe. Where do we go from here?

Klein: We have managed to narrow the window down. Just to give you an idea, prior to 1985 and the assay, there were over 4,000 cases of transfusion-transmitted HIV. Since the assay there have been 20. We would estimate, based on what we know, that there are maybe 200 infections per year in the United States, maybe slightly less than that. Half of those cases will die from whatever reason they have been transfused for, so there are very few infections. Hepatitis is still a big problem in the United States. There are now, as I said, better assays. The blood supply is better because of the better questioning that we do. If we could use a direct test for the virus…we tried one. We screened 520,000 units of blood with an HIV antigen test. It added nothing. But there is PCR (polymerase chain reaction), which detects the virus. In theory you could detect it within a couple of days of infection and therefore narrow the window of the donors dramatically. But this is not yet a test that can be used for screening purposes.

Harden: Thank you, Dr. Klein. We will continue this interview on another day.

This is a continuation of the interview with Dr. Harvey Klein, begun on 29 January 1993. The date is 8 February 1993. The topic of the interview is the history of AIDS at the NIH. The interviewers are Dr. Victoria A. Harden, Director of the NIH Historical Office and Dennis Rodrigues, Program Analyst.

Rodrigues: The last time that we talked you were telling us about platelet donation procedures that you had implemented I believe that they became standard once AIDS appeared and it was realized there was a greater risk.

Klein: Right.

Rodrigues: What was the motivation for the original employment of these techniques?

Klein: There were several. First of all we had, as I said I think the last time, about a 30-year interest in post-transfusion hepatitis. This is an interest that goes back to World War II in the Federal Government when there was a so-called icterogenic plasma. This was plasma that was made by the federal government for use in the war and resulted in large numbers of servicemen developing hepatitis. Back in the 1960s, this particular institution, the Blood Bank at NIH, became interested in post-transfusion hepatitis as "the" major problem with blood transfusion. We were always thinking in terms of infectious risk of blood, specifically of hepatitis, and multiple donors. One of the motivations was to decrease the number of donors for each patient. We believed, although there were few data to support the idea, that if we could decrease the number of donors we would decrease the risk to each patient. That was one reason for getting the largest number of platelets from a single individual.

A second reason was that the NIH began to use more and more platelets because of the kind of population it had. Patients had open heart surgery and patients had cancer. Both of those groups needed platelets. It was very difficult, even if you separated every unit of whole blood into its component parts, to have a reliable source of platelets, because platelets could only be stored for two days. You could store, at that time, red cells for three weeks—this is back in the 1960s and 1970s—and platelets for two days. Unless there was a more frequent source of platelets, red cells would be available but the platelets would be outdated. So we went to the so-called "single donor" platelets for both reasons.

Rodrigues: I have a question concerning an instrument, the IBM 229 separator, which you mentioned when we were talking about AIDS. Apparently someone at NIH collaborated in the development of this instrument. Could you tell us more about that instrument?

Klein: The first continuous flow blood cell separator was developed here at NIH in collaboration with IBM. Dr. Jay Freireich, who was here at the time, developed the NCI—IBM blood cell separator, and the story is an interesting one. It turned out that an engineer from IBM, Dr. George Judson, had a son with leukemia. The child was being taken care of at NIH, and the father came down to see him one time. The two major problems then in supporting kids with leukemia were infection and bleeding. As part of his tour of the facilities the father came through the Blood Bank and saw how blood was collected and separated out in centrifuges. As luck would have it, he had just finished working on a project at the University of Pennsylvania with a heart/lung machine. The heart/lung machine took large volumes of blood and pumped it around the heart and the lungs through an oxygenator in order to make open heart surgery possible. The IBM scientist was familiar with equipment that pumped blood around and oxygenated it. He looked at it and he said, "There ought to be a way that we could hook up a person to one of these machines and separate out the blood components, that is, take what we want and have everything else go back. It looks like all you really need is a centrifuge and a series of pumps similar to the heart/lung machine which used an oxygenator and a series of pumps."

Freireich, who at that time was a young investigator in the Cancer Institute (NCI), thought that sounded like a good idea. He went to his superior, a man by the name of (Dr.) Emil Frei—Frei and Freireich. Frei thought it was a good idea too, but he did not have much in the way of resources. So they put the idea to IBM who gave Judson a year's leave of absence to come to NIH and work with Freireich in developing this instrument.

They had made such promising advances at the end of the year that the Cancer Institute then let a contract with IBM, which resulted in the eventual development of the first continuous flow blood cell separator. So, it was an interesting, sort of serendipitous way in which that was developed. What they thought they would be able to do was collect white cells and platelets. It turned out to be probably more important for collecting platelets, but it was also important back then for collecting white cells to treat infection in leukemia patients, as well as collecting platelets to treat patients' bleeding problems when they were given chemotherapy.

A sidelight of that development is that the availability of that kind of instrument, not necessarily that particular instrument, has resulted in us being able to do gene therapy. In fact, what we do today is we separate out the cells and collect large numbers of lymphocytes with this kind of instrumentation and then we put genes into those cells as we grow them in the laboratory. Freireich's foresight back in the 1960s is still being capitalized upon in 1993.

Harden: I will reiterate that we should come back again and talk about hepatitis and gene therapy. You seem to be in a key position for many different things in terms of what goes on at NIH.

Klein: Yes. I think that is because the Blood Bank has donors coming in and we have to prepare blood components that go to patients and we have a large bank of specimens that we can freeze away. Many things that happen in the hospital sort of traverse these corridors and laboratories, and have over the years.

Harden: In our discussion of AIDS, if my memory is correct, we had just gotten to 1984 and the discovery of the virus, or at least the publication of the papers that made everybody accept that there was a virus. You had talked about the Blood Bank's—the Department of Transfusion Medicine's—efforts to inform donors, and separate out, or if possible, self-select, donors. You were starting to tell us more about that when the interview came to an end, if you have recalled specific things that you wanted to say, please do so. I am interested, again, in how donor forms got modified and what else you did.

Klein: Yes. I wish we had more of these donor forms available, because there was a constant process of modification. It is hard to look back now and appreciate what was going on. First of all, as I think I said the last time, the Government takes a long time to print cards. They have to be printed in large numbers. All of the information that we had, and had given to donors, will not exist on the printed cards, most of which are on microfilm. What we did, in order to respond more rapidly, was something like this. As soon as it appeared that was an increased risk in some activity, or an additional piece of information became available, we updated two kinds of materials. One was a booklet that we have used, and still have outside, which contained relatively short informational material, that was given to donors. We started this, I think, about the middle or first quarter of 1983 and continuously updated it. It was simply a piece of educational material. The second item that we had was a sheet that was a pseudo-legal document. It was always no more than a single page, always had a place for the donor's name, the date, and a witness's name and date. The witness, who was the screening person, would ask questions and the donor would then sign that the questions had been asked. The witness would also sign. Then, somewhere on the donor card, there has always been a statement like, "I have been asked and have understood all of the issues involved in blood transfusion," but it might not say, "I have been asked all the questions regarding AIDS." That might not appear on our donor cards.

Harden: I am a donor and I recall a list of questions on the donor card which, as far as I know, never refers to "AIDS" per se, although some of the symptoms are fairly recognizable. But there are other questions that might lead the

reader to think of hepatitis or malaria. "Have you traveled outside the country?" So the donor card speaks to a variety of diseases. Then there is the little yellow card that folds over. I asked particularly about why that was instituted.

Klein: Before we get to that one, let us get back to the regular donor card which now does say "AIDS" on it. But what it said is that, among the risk activities, is whether you are a gay male, or a man who has had sexual contact with another man since 1977. It also asks whether you have had contact with anyone who has had AIDS. The card lists the risk activities, and AIDS does appear and has since about 1985. I am not exactly sure when it was added to the card, as opposed to being added to, say, one of these throw-away pamphlets—it is not a throw-away; these were saved for a long period of time and then eventually discarded—but they were not part of the card.

The other card that you refer to is called the confidential unit exclusion, or CUE. We introduced those, I believe, toward the end of 1985. We introduced them in the belief that we might be getting individuals who are called in by us or who walk through the door. They sit down and we screen them, and sometime either during the course of screening, or after screening, it occurs to these individuals that, in fact, they are in a risk group but they just do not want to tell the screener. It is embarrassing for them, for whatever reason. So we, along with several other blood banks—the New York Blood Center, for example, was one of them—were relatively early in introducing confidential unit exclusion. The way we introduced it was to have a card that the donor would fill out that would say, "You can use my blood for transfusion, or you can use by blood only for research purposes." That card did not have a name on it; it only contained a number. The donor was required to fold up the card and turn it in. The card would be opened up in the laboratory, and if it said "Use my blood only for research," then that donor's blood would never be used for transfusion. In fact, that donor would be removed from the list of individuals who would be donating for patient purposes.

As with so many things that sound easy and wonderful, we found, after we started to look at the process, that a number of people simply did not understand the reason for it. Some felt, "Today I would like my blood to go to research, and next week I would like it to go to a patient." The actual method did not work perfectly. We changed the wording on the card several times in order to try to get the message across, and we still use a modified form like that, a confidential unit exclusion.

Harden: I presume you also find that as more and more people become sophisticated in understanding AIDS and about whether or not to exclude themselves, there are probably fewer instances where people realize half way through the form that they are in a risk group.

Klein: Yes. Some studies now suggest that this is no longer an effective way of screening out donors who are at risk. We will probably drop it as a way of proceeding simply because it does not seem to be effective any more. People are now much more aware of what the risks are.

There were several other ways of screening that we considered. One way was to give everyone a telephone number and say, "If you don't want your blood to be used for transfusion, call this number anytime of the day or night." We actually did a study calling blood centers around the country and sending them a questionnaire to see what the efficacy of the various methods of confidential unit exclusion were. We published the results in *Transfusion*. The call-back system does not work. So, not only did we institute a CUE, but we tried to evaluate the national effectiveness of CUE, and people simply did not call back. If you looked at the blood that was excluded and the blood that was accepted, you could see that the markers were higher, first of all, in blood where people self-excluded. Those units had higher markers for hepatitis and, in some instances, for HIV. In places that used the telephone call back, their percentage of unit exclusions was much lower and, in general, their markers were higher in the units that were being used. This suggested against that people simply did not take the trouble to call back. Once a person was out of the facility, if he or she had not done everything while there, that was sort of the end of it.

Harden: All of these units of blood, were, no matter what the donors put on the exclusion card, I presume, tested for HIV as soon as a test was developed. What happens in terms of the donor, if the donor has thought that he or she was not infected and then you get a positive test?

Klein: Now this is frequently misunderstood. The actual procedure is the following. The blood is tested for the antibody for HIV by what is known as an ELISA test. If the blood goes through the test and the test come back reactive, then that unit is retested in duplicate. If either of those duplicates is reactive, then the test is positive. If both of those duplicates are not reactive, then the unit is still discarded, but nothing is done with the donor.

If the unit is positive, because one of the duplicate tests has been reactive, we then call it repeatedly reactive. The first screen was reactive and one or more of the duplicates was reactive. If it was repeatedly reactive, then in this center we would send the specimen for an additional test. Some people have called it a confirmatory test, but the FDA (Food and Drug Administration) does not like that term. It is an additional test, which is called a Western blot. If the unit of blood is Western blot positive, we consider that a true infection. We would call the donor, or notify the donor, by asking the donor to come in, that he or she was infected with the virus. Automatically the donor would be eliminated from ever donating

blood, but the donor would also be counseled about what the test results meant.

In this institution we had a study for donors whose blood tests were positive for HIV and so the donor would be offered the opportunity to enter into a study for longitudinal follow-up.

Now, if the donor was repeatedly reactive with the ELISA test but this additional test, the Western blot, was negative, we would still, of course, not use the unit of blood. In the Blood Bank at NIH we also called in the donor. We would try to explain to the donor that he or she had a positive test but we were not sure that he or she was infected. It is very difficult to do. We had an enormous advantage because we could offer the donor the opportunity to be followed longitudinally with this as well. If the donor was at risk, was in fact infected, we would probably find that out. If the donor was not infected, we would probably find that out too. So at least the donor was under surveillance by what was, at the time, probably the most sophisticated laboratories in the country with regard to this issue and with the most knowledgeable physicians at the time in charge.

Other places faced a real dilemma. What should they do with a repeatedly reactive donor? Should they tell him or her that they were not sure that the donor was infected with the virus, but he or she should never show up again as a donor and that their blood could never be used again. A very difficult message. I think people tend to underestimate the impact that information has on an individual, on an individual's family and on an individual's practices, when he or she receives that message. In point of fact, with that kind of a laboratory result we did not know in 1985.

So institutions did not inform the donors. They did not use their blood. They did not call them back. The ethics of that, I think, are very controversial. If you do not really know what to tell the donors, what do you tell them? Many institutions elected not to tell them anything.

Harden: Can you describe, to take this one step further, who your donor population is primarily here? Are they NIH or other government employees, or do you have many non-federal people as well?

Klein: We have a very select donor population. For the whole blood part of the operation they are almost exclusively NIH employees. They have a mean educational level of sixteen years. They are interestingly enough equally divided between males and females, which is not what is found across the country. The percentage of ethnic minorities is in keeping with, or slightly higher, than the percentage of ethnic minorities in the regular population. By and large these are repeat donors who have been screened out over the years., some biologically. For example, if a patient develops hepatitis and got blood from one donor only, that donor is removed from the pool. If

that one donor is implicated in more than one case of hepatitis, that donor is removed from the pool. So we had a very safe pool of donors and, in fact, only two of the several thousand individuals on our donor rolls were infected with the AIDS virus.

Our platelets donors are drawn primarily from volunteers from Montgomery County. They too, over the years, have tended to be repeat donors and have been screened in multiple ways. The demographics are a slightly different. These donors have a slightly higher male to female ratio. They have a lower percentage of ethnic minorities. I honestly do no know the educational level, but they obviously are not as medically oriented as the population here in this institution.

Harden: Did a higher percentage of them turn out to be HIV-positive?

Klein: No, in fact, we have, I believe, only one in that group, again probably reflecting the fact that they are screened in multiple ways over the years and are volunteers.

Harden: As I recall, you not only followed your donor pool longitudinally, but you must also have followed the health care providers here in the Clinical Center who had had needlesticks and so on. Were you doing the laboratory work on that?

Klein: We collaborated on that, but we were not the lead group. Dr. David Henderson, in the Epidemiology Service, started those studies. We were obviously very interested in those studies and did all of the testing for them, and some of the counseling for the individuals. Unfortunately we had the first health worker in the hospital, and one of the first health care workers in the United States, to become definitely infected by a laboratory accident in our department. Ironically, it was a health worker who was a meticulous person and who did all the right things. She was handling a tube of blood from a known infected individual and was double-gloved. She removed the cap from the tube of blood—it was a rubber vacuum tube—and when she removed the cap, the lip of the tube broke off and the glass that was broken cut through her glove and cut her finger. Of course, we knew immediately that she was at risk and tested her. She unfortunately seroconverted in about eight weeks and sadly went on to develop the disease. So we were very much aware that this was a possibility and very interested, obviously, in what the risk was to our staff. As it turns out, the risk is relatively low, but we did not know that in 1985.

Harden: Your staff was, I presume, dealing with all sorts of different situations such as you described with vials of blood from infected individuals and with taking donors coming in, although with your population of donors it probably did not seem to be as great a risk.

Klein: That is right. I think we were able at least to say to our donor screeners and bleeders, that the people they were dealing with were relatively safe. They were probably safer than someone you might meet at a club at night in downtown D.C. But the patients in the Clinical Center—NIH was studying AIDS patients—were obviously a risk to the health care workers who were handling their specimens.

Harden: I comment on this because we have a friend who was a laboratory technician in our health maintenance organization. Apparently the organization did not tell the laboratory technician which blood was infected and which was not for a while. She was very worried about it.

Klein: We always told our staff that all blood was potentially dangerous. We told them that because of the hepatitis experience. We said, "Any blood that you see coming through here, no matter what we test it for, can transmit hepatitis, so you have to be careful." In fact, smoking in the laboratory, ever since I arrived here, and I am sure before that as well, was grounds for firing, certainly grounds for removal from the laboratory. Eating in the laboratory was absolutely forbidden for any reason. Storing food in a refrigerator in a laboratory where blood might be stored again merited just about the most severe penalty for these kinds of actions. We realized very early that our staff was at risk for hepatitis and, in fact, many of our staff were infected with hepatitis B because, as it turns out, that particular virus is much more infectious than HIV is. But the fact that if you were stuck with a hepatitis B positive needle, your chances of becoming infected were somewhere between 15 and 30 percent—and because we did not know what the risk was from the AIDS agent—made us incredibly cautious about that in the very early days. It turns out, fortunately, that HIV is much less infectious, but unfortunately, of course, we saw the results of an exposure in our laboratory.

Harden: Can you give me a percentage for HIV?

Klein: Yes. About 0.5 percent of known positive needlesticks seroconvert. About 0.5 percent, 5 per 1,000, compared to, say, somewhere between 15 and 30 per 100 with hepatitis B.

Harden: From the time that the virus was identified, you had a known agent to react. Would you describe what steps you took with regard to collecting blood, and what experiments you were involved with?

Klein: I think I told you in the first interview that we did go back to our frozen specimens and we did find two donors who were positive. We followed the specimens of the recipients of their blood and demonstrated that, in fact, those donors had infected the recipients. We defined the period of

latency between the time a patient was transfused and the time the test became positive, and that was about six to eight weeks.

The second thing that we were able to define from those specimens, was we had some individuals—donors—whose specimens tested positive by the ELISA test but did not test positive by the additional test, the Western blot. In fact the recipients of their blood did not become infected. That, again, was immediate, very reassuring information that these were false-positives and that we were not seeing more real infections than we had thought. Those studies were very important.

I told you about the studies with the chimpanzees that were very important for a couple of reasons. They demonstrated, first of all, that blood transmitted the virus unequivocally to another primate, and they established the fact that the chimpanzee was a model for research.

After the advent of the HIV test another extremely important study that we jumped right in to was we said, "We would like to know the natural history, or what happens, with these donors who are positive." All of the data that had been collected previously was from individuals, gay males, who had been picked up either because they had become sick, or because they were in a cohort of gay males that was being studied. No one had really prospectively followed healthy blood donors before.

So we called up the Regional Red Cross and we said, "We would like you to send up any true positives that you have, and we will repeat the testing if you do not want to do additional testing. As controls we would also like to follow some of these people we think are false-positives, some of the ELISA repeat reactive that are Western blot negatives. We want to know whether these people go on to get the disease." The Red Cross agreed to do that. As I said, we had very few in our NIH donor population, but the Red Cross had hundreds. They asked everyone who was positive whether they would be willing to participate in the NIH study. By participating in the NIH study they would come to NIH, be retested, have a battery of other tests, have a complete history and physical examination done by a physician, and they would be followed every six months. They would not be treated with anything because there was not anything to treat them with. About all the benefit they would get out of this was that they would receive the information that was available as soon as there was information available, because at that time federal government was really on the cutting edge of everything, and people looked to NIH for information. About half of all the positives agreed to do it. The other half did not want to do it.

Harden: Was this the Washington D.C. Red Cross?

Klein: The D.C. Red Cross. There were about 170 people who were true

positives, and we got another 60 or so who were false-positives. We could have gotten many more of them, but that was a sufficient number for the study, and this was a major undertaking for us.

We did something that was a first-time-ever at NIH, I believe, which was novel and difficult, and that is, we established a totally separate numbering system for these individuals outside of their hospital records so that no one could retrieve the results. I am sure that you recall the hysteria involved with identifying a person who was positive for the AIDS test, and there were federal regulations about releasing the identity or invading the privacy of an individual. We were able to set up a system where subjects were followed at NIH, but were followed with a completely different numbering system. They did not have a hospital number, and could not have their information retrieved by anyone but a small, select set of investigators. Going through the IRBs (Institutional Review Boards) and the ethics committees, this was very difficult to do. There were many arguments about how this should be set up and whether it should be set up, but it was, and it remains until this day.

Those true positives and false-positives have been followed now since March of 1985. This is the largest series. The individuals were seen every six months. Specimens of serum, cells, and nucleic acid were frozen away, so that should additional testing be useful for the effort against AIDS, we would have those specimens over time in an interesting cohort of individuals. It has been a very helpful study from a variety of standpoints. First of all, it did define the fact that people who were false-positive by this assay did not get sick; that their immunologic status did not change; that they remained entirely normal. You could only say that after following a group for about five years. Prior to that you could guess. From our refrigerated and frozen specimens you had a pretty good idea. But this was the first prospectively followed cohort, so they did not get sick. The true positives, of course, did, and about 16 percent per year developed frank AIDS.

The other aspect that was important was looking at the demographics of the people who came into the study, again realizing that this was not a randomized group but a self-selected group. We did not know what made one person say, "I am never going to call them at NIH." But what we found out was that a high percentage were African Americans. This does not seem surprising in 1993, but in 1985 there were people who were saying that black Americans did not become infected with this virus, that this was a white, gay male disease.

Harden: You are certainly aware of the Tuskeegee syphilis experiment?

Klein: Absolutely.

Harden: There is a group at the University of Maryland which published a paper in the *American Journal of Public Health* in 1992 saying that part of the reason African Americans may have said that they did not do this was a left over fear of being in federal government studies. Apparently there was even an impression that the federal government has given the men at Tuskeegee syphilis. Did you hear anything like this, or about this?

Klein: Not from our group of individuals. At the time, of course, we had to talk to all of our donors about the rumors going around that HIV was a virus developed by CIA. One rumor was that it was developed up in Frederick, that it had gone to Africa first via the CIA, second via vaccines that had been used for polio testing in third world countries. We did hear all of these rumors, but none of the people that came to see us really believed any of those things. A high percentage turned out to be gay males and they were black gay males. But at the time—it seems foolish today—people felt that if you were black you were somehow protected. That was actually being said. While we had never believed that, here were data to look at. Now, our sample was clearly biased in that it came from Washington, D.C., where a high percentage of blood donors was likely to be African American. If you were young, black, and certainly if you were a gay male, you were at risk in our sample.

We had an opportunity to follow these people over time and see what happened to them in terms of their immune status, in terms of developing frank AIDS, and, unfortunately, in terms of dying. What we found, as you might guess, is that about 12 percent per year of those who developed AIDS died.

As we continue this study now, of course, these individuals have been offered AZT or ddI, and they have been offered participation in other NIH therapeutic studies when those have become available. There has been some benefit to these individuals whom we have followed over the years and have been so helpful to us.

We found out a lot about their sexual practices. One of the things that was very unfortunate, and again seems hard to understand in 1993, was that when we started our studies we desperately wanted a psychiatric component to the study and were unable to get one. We wanted psychiatrists involved for two reasons. We wanted to find out something about why these individuals had donated blood, since they were being screened with questions and so on and still had donated. We also wanted to have that as a resource, realizing that a positive test result as a tremendous psychological blow for someone. We could not find a group within the federal government that was interested in following these individuals. We tried people at NIH, and the Department of Defense, and we simply could not find anyone who was willing to devote the resources in 1985 to a brand new cohort of individuals about to be told that they had

AIDS, or a virus that frequently resulted in AIDS, and that they were going to be followed prospectively along with controls. To this day I feel that this as one of the great lost opportunities to find out about peoples' attitudes, how they were affected initially and how they changed over time.

Harden: Did people give you a reason about why there were not interested?

Klein: We were told by some groups that it was simply too expensive. They did not have the time and the personnel to devote to such an investigation. We were given the impression that it probably was not a very high priority at the time. I was astonished. Of course, we had no problem getting immunologists, and the FDA (Food and Drug Administration) was extremely interested both in the specimens and the data that were coming out of the demographics from these individuals. We learned very quickly what was wrong with some of the questions we were asking. We also learned that about a quarter of our people had gone to donate blood at the Red Cross simply to be tested. We had feared that that would be the case when a test came out. Alternate test sites had been set up. But still people came to be tested. When we asked them why they came to the Red Cross instead of going to the alternative test sites, they told us that it was more pleasant to come to a blood center, and frankly, it was more confidential. So there were a fair number of demographic points that came out of that study. It was a very important study, one that continues. I believe that the freezer full of specimens will also turn out to be valuable as the years go by.

Rodrigues: One other question, but related to AIDS, but you mentioned last time some of the other devices you had. I am always interested in technologies that are developed at NIH. Other than the story that you told us about the blood separator, are there other projects that your department is undertaking in terms of developing new technologies?

Klein: I am not sure that it is new technology, but since the late 1960s blood has been stored in plastic bags—red cells, plasma and platelets. We have studied the platelets here, and many other studies have been done on gas exchange through the plastic. It is a very important subject. When you collect a bag of platelets, they are best stored at room temperature, and you rock them so that there is gas exchange through the plastic bag. When Dr. Steven Rosenberg started doing his studies of LAK cells—that would have been in the early 1980s—he was originally growing his cells in what are known as roller bottles. They are firm plastic bottles. You could only grow limited number of cells. There is no air exchange through the plastic. He has walls and walls of these roller bottles. They are very difficult to work with, and the chances of contaminating the roller bottles when you went into them to change medium was enormous. Dealing with human beings, growing up cells in these bottles, and making a product that you then gave back to human beings, was a very tedious process. At that

time people would come to see what Steve was doing and they would leave and say, "We can't do that at our institution. We don't have the resources."

We had an idea, working with Steve. We had been collecting the cells from his patients, and we said, "We store platelets in these bags. Why can't you store your cells and grow them up and expand them in these plastic bags? It seems to make a lot of sense. They exchange gas very well. If you did that, you could change your medium and put in your additives much the same way we make blood components. You could spin them down in a centrifuge and you could squeeze out supernatants that you do not want. Then you can connect these bags in a sterile manner through their plastic tails without ever opening the system."

It took quite some time to convince Steve Rosenberg of that, and of course he had to do the studies with his cells in his laboratory, which took even longer. But eventually he agreed that this was the way to go, and it had enormous advantages. All these bags could be processed with our automated equipment. He switched entirely from roller bottles to plastic bags. This had two major effects. First, it allowed him to do much more than he could do previously with fewer resources and with a much greater safety margin. Instead of having 4,000 openings per patient in a system, he was down to a half dozen to a dozen openings, so the risk of contamination was much smaller. The other advantage, certainly for the advancement of that kind of treatment, was that it allowed other people to do it as well. People could come to the laboratory and say, "We can test this in our medial center." In fact, within a year, NCI had set up half a dozen extramural centers testing LAK cell therapy. It would not have been possible without those bags.

The bag system is now being used for gene therapy and it was used for the first gene therapy patients. We are not using it for growing up the vectors for the gene therapies, all of the cells, for the patients. Sterile docking connections can be made and the risks of infection and losing these valuable biologics have literally disappeared. So I think that was a major contribution coming from blood banking technology being applied to new therapies and new ideas.

Harden: Is there anything else that we need to cover?

Klein: I think in terms of the response to AIDS, I want to emphasize again that we believe that questioning and understanding the behaviors and the demographics of the epidemic are as important as the actual testing part, or screening. We learned from hepatitis, where getting rid of paid donors and then finding out what kinds of things correlated with hepatitis, that questioning and demographics were just as important as testing was. Over the 1984-1993 period we have—as have others—repeatedly updated and

improved our questioning. We learned, for example, as did others, that bisexuals do not consider themselves gay. If you had to ask about contact with another man, asking, "Are you a homosexual," or "Are you a gay male?" were bad questions, and we missed people. We found that out in our prospective studies of donors from the Red Cross, by asking, "Why did you come? You knew that you were a gay male." The answer was "I am not a gay male; I am bisexual."

We continually updated our questions as we learned more from these studies. Our actual screening techniques that are in addition to testing have become much more sophisticated and much more effective. That is a very important point, because many people felt that with the test that would solve the problem. It has not. We still have some cases of HIV-infected donors that slip through the tests. We hope that the improved screening techniques eliminate more who would have slipped through the testing.

Harden: What do you see as the future in terms of blood substitutes and other ways to eliminate the very small percentage of HIV-infected donors that still remains?

Klein: What would be ideal is either to sterilize blood from all infectious agents, or find some kind of a substitute for the various components of blood. It is possible now to sterilize plasma, at least there is a research publication on sterilizing frozen plasma, and I believe within the next year, all of the plasma that we use will be sterilized. Commercial companies sterilize a variety of factors for hemophiliacs. We cannot yet sterilize cellular components—red cells and platelets. It looks as if it will be a difficult chore to be able to sterilize those components without affecting the infection of the cells. There is a lot of work being done, but I am not optimistic that within the next several years we will be able to sterilize those cellular components.

Harden: So, how about using an artificial component or stem cell research?

Klein: Stem cell research, I think, is very exciting. Just as we can now grow up all kinds of cells in incubators, it is certainly possible that we will be able to take very early progenitor cells and make all kinds of blood cells. Bear in mind that if you start with a human cell it does not guarantee that you will not have some kind of an infectious agent. Since cell culture systems are ideal for growing viruses—that is how we have done it all these years—viruses could also be introduced. It is not perfect but it is very promising, although again it is a long-term prospect for growing blood for human use. Certainly it is feasible, whereas a decade ago I think everyone would have laughed at the concept. No one is laughing any more.

There are promising substitutes for red cells, that is, components that will deliver oxygen. Molecular technology has allowed us—us being the community and not the NIH—to clone the gene for human hemoglobin and now to produce hemoglobin and grow it up in large vats much like making beer or growing beer. Human hemoglobin can be grown and a couple of tricks have been applied to make the hemoglobin more desirable for transporting oxygen in human beings outside of the red cell membrane. It still remains to be seen as to whether that will be toxic, and there are several groups working very hard on that. My guess is that within the next year to two years either we will have a red cell substitute from the hemoglobin protein, or we will know that we will never have a red cell substitute because the hemoglobin itself is endogenously toxic. But again, five years ago I would have said that we were not going to see any of that in the near future and we will not know the answer to that.

There are also some other chemicals that carry oxygen. At least one of them has been licensed in cardiac surgery for coronary artery surgery, not as a blood substitute, but as an oxygen-carrying radiopaque fluid. Work in that area suggests that perhaps within a couple of years we will have something that at least transiently will carry oxygen and might eliminate about half of the blood we use during surgery, a short-term substitute. Since most of blood in the United States that is used today is still used for surgical procedures, that would be a major step forward.

I do not think in my lifetime that we will have a replacement for the clotting cells, for the platelets. There I think the hope is either to be able to grow them in culture—and I think that is a ways off—or be able to put into human beings early cells that will then become platelets. We are seeing that already in some of our cancer therapy, where early progenitor cells that circulate in the periphery can be collected from a patient, frozen away, given aggressive cancer chemotherapy, and then these progenitors given back. In 10 to 15 days there will be some platelets and white cells from those progenitors, while platelets cannot be frozen very well and white cells not at all. This has not totally replaced the transfused platelets, but it has shortened the period of time in which platelets and white cells are needed from perhaps twenty days, maybe even four weeks, to perhaps five to ten days, which again is a dramatic advance. We have seen the kind of technology that will cut down on the need for transfused blood components and use the patient's own cells to get them through other procedures.

Harden: Thank you, Dr. Klein, for talking with us.

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