

Dr. Harvey Alter
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Bethesda, Maryland
Interviewer: Jessie Saul

Saul: I'd like to talk today about your work with hepatitis and your research experience, particularly dealing with safety issues. I'm interested in hearing how hepatitis was seen as a safety concern for blood transfusion in the first place, and then safety practices dealing with the hepatitis-infected samples. Now, I know that you came to the NIH in the 1960s as a clinical associate.

Alter: As a mere child.

Saul: A mere child.

Alter: Yeah.

Saul: How did you end up here, and what was your path that led you here?

Alter: Well, my path was that I had intended to come to NIH. I was in my first year of residency at the University of Rochester, Strong Memorial Hospital.

Saul: Rochester, New York?

Alter: Rochester, New York. And my intent was to go to NIH because that was an academic pathway, if you could get into NIH. It was just what people did, much more so than now. But I hadn't gotten my application in on time. Actually, I had gotten my application in, but it had not yet been acted on, when I got a letter that began, "Greetings," and contained a token taped to the letter, saying, "Report to Fort Dix, New Jersey," because I was from New York City, "on November 28th," I think it' was. And people were being called out of residencies. Interns were still protected, but first-year residents were considered expendable. I was at Rochester, and several people got similar letters. So I began some frantic calls because I really want to come to NIH, but I hadn't yet been commissioned. Several people interceded for me. The long shot was that Dr. Scott Swisher, who was the head of hematology at Georgetown, was on a lot of committees for what was the current FDA but was then called the Division of Biologic Standards (DBS). And he got me to be able to come to the Blood Bank, which at that time was under DBS. And the Army said that if you report to the Public Health Service before the date you're supposed to report to the Army, then you're okay. So I left my residency midyear and ultimately made that up by staying at NIH two and a half years instead of the usual two years.

Alter: So I would have gotten here in the normal course anyway, but had I gotten drafted, my life would have been totally different. I probably would not have wound up in a research career. All through my life, little things have turned it around. At that particular time (that year), this was the best thing that ever happened, because I was working to try to figure out why people got febrile reactions from blood. We already knew about red cell antibodies, and we knew about some white cell antibodies, though those weren't very well worked out at that time. But my thought was that maybe people react to plasma proteins that might be different than their own. So I set up these little agar plates in which I would take the serum of somebody who was repeatedly transfused - these agar plates in which you punch wells, called Ouchterlony plates, but you made them yourself. And you would surround this person with, say, six other people, normal donors or whatever, and if these people had antibody against the normal donors, then the antigen to the antibodies would diffuse in the agar. Where they met, you'd get a precipitant line. I had these plates piled up all over the desk, and one day Dick Aster, who was at that time working in the blood bank on platelets and has since become one of the world's leaders in platelets, he said, "I attended a very interesting lecture today. And the guy is doing the same thing you're doing." And he said, "It was Baruch Blumberg, and you ought to go talk to him because he's setting up agar plates and he's finding some precipitant lines."

So I went to Blumberg probably the next day, and that was one of the beauties of NIH: so many people doing so many things, and if you want to work with somebody, you can just talk to them. In those days it was particularly easy to set up collaborations. So by the next day we had a collaboration, and for Dr. Blumberg it was very useful. He was a geneticist. So he was looking for polymorphisms, serum protein polymorphisms, that is, a protein that exists in multiple forms and is maintained in the population sort of like sickle cell is maintained in the population because it gives some selective advantage even though it can be lethal, but gave a selective advantage in Africa. So anyway, he was looking at it from a genetic standpoint and I was looking from a blood bank standpoint, and we began to work together. He had already discovered a polymorphic system in human beta lipoproteins, so if you reacted one person[']s blood serum] with another [person's], you found that periodically this transfused patient would have a line against another patient, and that line would stain blue because it contained lipids. We were working to characterize these beta lipoprotein polymorphisms, and, in fact, published on that, when one day I saw a line. You could first see the lines as just milky white, and then you stained them for lipid. And we saw this milky-white line, but it didn't stain for lipid, or did very, very faintly. And then we counter-stained for protein using a stain that turned red when you have protein. The line was intensely red, and that was a new line. As it turns out, we found that that line was a reaction between a hemophiliac who'd been multiply transfused and an Australian aborigine. Blumberg had these huge freezers full of samples from all over the world, and so one day we would test Samoans and one day

we'd test American blacks and another day we'd test Australian aborigines, and that was who happened to come up that day. So now we had this new line...

Saul: Can I just ask a quick question?

Alter: Sure.

Saul: The multiply-transfused people, yeah, I think I have that picture.

Alter: Oh, you have that one. Yeah.

Saul: It's a great picture.

Alter: That was me when I was young.

Saul: The reason you're using multiply-transfused people is because they already had a lot of antibodies built up.

Alter: Well, they had the potential to have a lot of antibodies. They had a lot of exposures.

Saul: Okay.

Alter: We were looking for them to develop antibodies to things different than themselves.

Saul: All right.

Alter: And we figured the more you got transfused, the more likely that would be to happen.

Saul: So then you were checking to see which of those antibodies had actually developed in these people.

Alter: Well, first to see if you get a line in the agar, then you assume that an antigen-antibody reaction took place. Now, it was possible that the people in the outside world had antibody against the hemophiliac, so later on you had to show that the reaction occurred from the gamma globulin of the hemophiliac, so we did that.

But it was just that this particular patient who had been multiply transfused was reacting to some protein in a presumed "normal" aborigine, and that's what we knew at that point. We originally called it the red antigen just by its staining characteristics, and later on debated whether to call it the Australia antigen for the person in whom it was discovered or the Bethesda antigen for the place where it was discovered. And Blumberg said that the newly discovered hemoglobins were being named after the city of the patient or the place of the patient, so we went that route. In the end it would have been better if we had named it Bethesda antigen because it later got a little murky where this thing was actually

discovered — maybe you don't want to put that in — because Blumberg moved to Philadelphia a little bit later, and the rest of the work was continued there.

Alter: So at that time, in the early 1960s, we had this new antigen, and then the question was, what does it mean? And the first question was really, how frequently does it occur? So we then, using that same hemophilic serum, we then started to screen patient populations, and we found pretty low - we found only one in a thousand normal donors had the antigen, but it was present in the donor population.

When we started to screen patients, we found that about 10 percent of leukemia patients had the antigen, so it looked like there might have been some link to leukemia. It wasn't clear what that was at that time. So the first publication on this antigen actually said "a new antigen in leukemia sera" and postulated that maybe this is somehow related to the agent of leukemia. It's always been thought that leukemia might be a virus. We didn't look for viruses at the time. We talked about it. If we had done electron microscopy at that time, looking for viruses, we would have actually seen this antigen because it was present in very big quantities. It got done later, but it would have probably saved about five years in this story. What we really had was an antigen that seemed related to leukemia. I had done some biophysical characterizations of it, and it looked like it was relatively low density, etc., so we had some characteristics of it were that it sedimented.

But at that point, my time at NIH was up. Blumberg was moving to the Institute of Cancer Research in Philadelphia, and he asked me to come with him, but I wanted to finish my clinical training. So I went to the University of Washington in Seattle to do a second-year residency, and I finished the paper during that year since we hadn't quite completed the paper.

And then, meanwhile, Blumberg continued to work in Philadelphia. He's a very persistent kind of guy, because this was a finding that was interesting, but since it wasn't definitively linked to anything, it could have been kind of dropped. But he kept pursuing it and kept making hypotheses and then testing them. So a lot of wrong hypotheses actually led to the right answer.

This whole story is one of serendipity because we weren't looking for a hepatitis agent. He was looking for genetic things and I was looking for blood bank things, and neither one of us knew anything about liver disease. So it is a very good example of scientific serendipity.

Blumberg made this hypothesis that if this is a disease that is genetically determined — and as a geneticist, he thought it was — and it's associated with leukemia, let's look at people who have a genetic predisposition to leukemia. One patient population that has that [predisposition] are patients with Down syndrome, which was mongolism in those

days. So he looked at a group of patients with Down syndrome, and he found that overall about 10 percent of them had the Australia antigen - exactly the same proportion as the patients with leukemia. I'll get back to why leukemia was important later. So this fit right in with his hypothesis, but I give him a lot of credit that he didn't just accept that. He then looked at patients with Down syndrome in different settings. When he looked at them who were institutionalized in large institutions, about 30 percent had the antigen, and in the smaller institutions, it was something like 10 percent. But among children who lived at home with their parents, it was under 1 percent. And among newborn Down's patients, it was zero percent. So this said that it's not something they're born with, and it seems to relate to their environment. Since it's very prevalent in big institutions, which are known to harbor all kinds of infectious agents, this was the first clue that this might have been an infectious antigen.

Then another serendipitous thing that happened was that a technologist in Blumberg's lab, her name was Barbara Werner, and Barbara Werner had come over to my lab. She had been at NIH with Blumberg and I was showing her how to do the agar gel diffusion test. Well, later on, she was working in the lab with Blumberg in Philadelphia, and she turned yellow. She was coming down with acute hepatitis. They drew some blood from her, and, among other things, they tested her for Australia antigen, and she was positive, whereas she had been previously a negative control in their lab. This suddenly made sense that this antigen was somehow related to hepatitis, and then they tested other patients with hepatitis and other Down's patients and were able to show this was a hepatitis antigen. In retrospect, the leukemia patients had it, not because of anything to do with leukemia, but because they were multiply transfused and they were immunodeficient, immunosuppressed, so that when they got the virus, they couldn't get rid of it, and that's true to this day. So you saw the pieces then fit in, and I explained the Down's patients, explained the leukemia patients, and it suggested that this antigen was the hepatitis virus. Ultimately, it got shown that it was the surface coating of the hepatitis B virus. I wasn't involved in that part of the story. I was involved in the beginning, but not that middle that linked it up to hepatitis.

But by that point, I was at Georgetown doing a hematology fellowship, and then I was on the faculty of Georgetown, and there was an opportunity to come back here to the Blood Bank, and particularly now to look at post-transfusion hepatitis. I took that opportunity and I came here, and the NIH had already started these prospective studies of post-transfusion hepatitis, and I took over that project and expanded it. Basically, we looked at people who were undergoing open-heart surgery and prospectively followed them every week or two after transfusion for a whole six months; every week or two for the first three months and then monthly for another three months.

Saul: Why was it open-heart patients?

Alter: Well, we did that because they were a nice, clean population. They got a lot of blood all in one day. They didn't have any underlying malignancies or immunodeficiencies, so that if something happened to them hepatitis-wise, it was probably due to the blood. In addition, it would probably show up because they were not going to die from a malignancy. So it was a very clean population.

So later on, about 10 years ago, they disbanded the heart surgery program here, and it really severely impacted on our studies. We had to go scouring around the city to get other populations.

Saul: When did they do that?

Alter: I think around 1990, maybe a little earlier.

Saul: Was hepatitis considered to be a public health concern? And why do post-transfusion studies of it?

Alter: Well, it was known to be a significant transfusion-related problem. It was known from World War II that blood would transmit hepatitis, and a lot of soldiers were infected. They were infected by vaccines that were contaminated with plasma. It was just a known risk of transfusion, but the extent of the risk was not known. And the data from these studies was kind of astounding: prior to 1970, we showed that over 30 percent, about 33 percent of patients undergoing open-heart surgery here got hepatitis. The reason we were picking up such a high rate was that we were looking for the first time for biochemical evidence of hepatitis.

Saul: Not just clinical evidence.

Alter: Yes. If you wait for a patient to get jaundice, only a minority of patients with hepatitis ever get jaundice. And if the jaundice happens after an incubation period, they're usually home by that time, and nobody ever traces it, thinks about it as related to the transfusion, so it doesn't get back to the place that transfused them. But by looking at them prospectively, you picked up enzyme elevations that indicated hepatitis and you picked up, of course, all the clinical cases as well. So that was the main reason I think we were finding so many cases.

But also these patients, because of the heart-lung machine, got 17 units of blood each on average, so it was a huge exposure risk. And Dr. Walsh, John Walsh, who'd been here, Dr. Holland, and Dr. Schmidt had already shown that if you got a unit of paid-donor blood, that you had about a 50 percent chance of getting hepatitis. In other words, if the blood was purchased from outside sources, you had about a 50 percent chance of getting

hepatitis, whereas if you got only volunteer blood, it was something like a seven percent chance, so there was this dramatic difference.

Alter: So in 1970, we had these numbers. We now knew that a third of our patients were getting hepatitis - an occasional one was getting very severe hepatitis - and that the risk was really related to the source of the blood. Now, we were buying about half our blood at that time from outside sources, primarily from a place in Baltimore and another place in Memphis. These were classic, commercial blood establishments where the donors really were derelict and selling their blood as much as they could to get money to buy alcohol mostly, but maybe even in those days, it might have been drugs. We don't know.

I remember meeting in Dr. Schmidt's office. Dr. Schmidt was the head of the Blood Bank in those days, Paul Schmidt. He and Dr. Holland, who was the assistant chief, and myself, we all concluded that we could not tolerate rates of hepatitis like this, and we had to switch to an all-volunteer donor system. We didn't know how we'd get the blood because supplying 17 units per case, in addition to everything else, was a lot. Anyway, we found ways to up the blood procurement.

Saul: How did you do that [up the blood procurement]?

Alter: Well, at first we switched to a system whereby we, the first unit you donated had to be voluntary, and the second unit you got paid for, because we were afraid we would just crash without it. But very rapidly we were able to go to an all-volunteer system within that first year.

Saul: Was that through the Baltimore program?

Alter: No, no. We started it here.

Saul: It was here.

Alter: We expanded our own donor program. We first had to switch in payment- you had to volunteer the first and every other time. Then we went to all volunteer. We cut out Baltimore. We relied more on the Red Cross, but we couldn't rely completely on them. We wanted to be self-sufficient, and the Red Cross wasn't as efficient in those days as it is now. They couldn't supply us as well. So I would say in less than a year, we were into an all-volunteer system, and it was working fine. And then we used the Red Cross as a backup if we couldn't meet demands.

Probably nothing we've ever done had so much impact, because we were starting at such a high level. But we actually did two things at once. We switched to an all-volunteer system, and we introduced the first test for hepatitis B, the Australia antigen test. I think we were one of the first places in the country to adopt it as a routine. In fact, we started

out using that same agar-gel diffusion as the way to find it. But then companies came in and they developed sort of electric, electrophoretic.. They called it counter-lectrophoresis. And then, subsequently, better tests came along. So by the end of 1970, we were now doing hepatitis B testing, we were [using] all-volunteer blood, and we showed that our rates dropped down from 30 percent to about 11 percent. I think that's about a 70 percent reduction.

Saul: Were different hospitals and the blood banks around here and around the country dealing with a similar type of thing?

Alter: Yes. Nobody realized the rates were so high, but with these data, by 1971, I think the whole country was doing hepatitis B testing. I don't remember what year everybody switched to volunteer-donor blood, but it was soon thereafter. A lot of places had already been in volunteer-donor blood before us, so we weren't the first to do that. But it became mandatory from the FDA around 1971 or 1972.

Saul: They had to label, I think, starting in 1972.

Alter: Okay. So, you know, once you label, it's the same as saying you can't use it [blood from paid donors] because nobody wants to label this as bad blood. So it was 1972. Okay.

We started [using only unpaid donors] in 1970. There had been other proponents of an all-volunteer blood system. One of them, interestingly, was a surgeon. Our surgeons certainly weren't very perturbed by the high rates of hepatitis because it happened months after the patients went home. They didn't hear about most of it.

Anyway, the whole country now was doing hepatitis B testing and using volunteer donors, and that had a tremendous impact.

Because we stored all these samples [of blood from open heart surgery patients], as the hepatitis B test got better, for example Abbott Laboratories developed radioimmune assays and ELISA assays that were quite sensitive, we were able to go back into the stored samples. With the more sensitive tests, we were able to show that when the rates were 30 percent or higher and we had no hepatitis testing, still only about 20 percent, 25 percent max, of the cases were due to hepatitis B. That was the first clue that we had a big non-B hepatitis [problem]. And then in 1973, I think it was, here at NIH, we'd been a big collaborator with Dr. [Robert] Purcell at NIAID [National Institute of Allergy and Infectious Disease], and [Dr. Stephen] Steve Feinstone was working in Dr. Purcell's lab. And Feinstone and Kapikian, Dr. Albert Kapikian, and Purcell discovered the hepatitis A virus. We're all still here at the NIH, in fact. Feinstone was looking through stool samples from hepatitis A epidemics by a technique called immune electron microscopy. He found these particles which turned out to be hepatitis A. And then we could do a hepatitis A

test. It was a very crude test, but you could do it. So we went into these non-B samples and looked for hepatitis A, and at that time there were only two known hepatitis agents, [hepatitis] A, the infectious hepatitis virus, and [hepatitis] B, the serum hepatitis virus.

Alter: So we went in and were kind of surprised that not a single case was hepatitis A. It shouldn't have been that surprising because epidemiologically, they [the cases] weren't like hepatitis A. But we assumed that some of these at least would be hepatitis A. But none of them were. It was then, with Dr. Purcell and Dr. Feinstone, that we - and I don't know who's responsible for this - but we came up with this non-A/non-B hepatitis [nomenclature]. I do remember that Purcell was the one who was cautious and said "we shouldn't call this hepatitis C as yet because we haven't proven it's a virus. If it is a virus, we don't know how many different viruses it is, so it's better to just call it what it isn't."

Saul: Which you knew.

Alter: Which you knew, yeah. That was a very awkward name, but it was the right way to go. We all assumed, "Well, we'll find it very shortly," but we didn't. So that was the beginning of non-A/non-B [hepatitis].

Then, in 1975, people had done some experiments trying to transmit non-A/non-B [hepatitis] to chimps or other animals and couldn't do it. And my presumption was, well, take the very best cases. We had some really well-defined cases [of hepatitis] now that we had prospectively followed. Take the best cases. We'll use a large volume and we'll give it to a chimp. And we picked five cases, went into five chimps, and all five chimps came down with biochemical evidence of hepatitis. Chimps don't get clinical hepatitis, which was nice. So none of them got sick, but you could show they all had clear-cut hepatitis. So that was the first proof that non-A/non-B hepatitis was [caused by] a transmissible agent.

Saul: What was the importance of having the chimp model?

Alter: First of all, it was to prove... Because there was no way to culture. You couldn't see this virus; you couldn't culture the virus.

Saul: And there was no test for it?

Alter: No. You had no test for it. So the chimp was a way to show that you could transmit [the virus from one person or animal to another]. There was an outcome you could measure, which was elevations of enzymes, liver enzymes, in the chimp, the same as you get in humans. You get elevations of serum, what we now call ALT, alanine amino transferase. It used to be called SGPT.

The importance of the chimp was that now you had an animal that you knew you could infect, so then you could use that endpoint to see what you could do to the virus to make it noninfectious. Again, studies were mostly coming out of Dr. Purcell's lab, but we were all collaborating. We had actually characterized this one patient who had a particularly high titer of non-A/non-B. Patient H became a famous patient. The H strain. And patient H could be diluted over a million times, and you could dilute it a million times and then put 1 ml into a chimp and still infect the chimp. So this became the prototype challenge inoculant.

Then Dr. Feinstone and Dr. Purcell treated H serum with chloroform, which destroys lipid membranes. It's a way of characterizing viruses into whether they have an [lipid] envelope or not. And you could show that when you treated [the serum] with chloroform, it was no longer infectious. So now we knew that this was an envelope virus. Then another fellow, a Japanese fellow in Dr. Purcell's lab, Li Fang He, did filtration studies, and you could show that if you use filters of different sizes, if you put it through a big filter, it was still infectious; and the next size filter, it was still infectious. But then you got down to a 50-nanometer filter and it no longer passed through. So with that, you could size the virus. So that made it a 50- to 60-nanometer virus that had an envelope.

Saul: A lipid envelope?

Alter: A lipid envelope. So it told you a lot about it. But, still, we were unable to develop a test, and our presumption was that the virus didn't [produce a large amount of antigen], as opposed to hepatitis B, where the virus is highly defective and it produces a huge amount of antigen over and above the actual virions. [We thought that] the reason we were able to pick up [hepatitis] B with agar-gel diffusion, which [is a] very insensitive technique, [was that] there was just so much protein around. But that wasn't clearly the case with non-A/non-B. And then we began to wonder, "well, maybe people don't even develop antibodies to this." We were wrong. They do. But we couldn't...

Saul: find the antibody?

Alter: No. Actually, we couldn't find the antibody because we didn't have an antigen, is what it turned out to be.

So we tried over the years, in the 1980s, we tried everything that was then available to look for this virus, as did a lot of people. In fact, so many people published that they thought they had a non-A/non-B agent that I developed this panel of using the samples that we knew were infectious in the chimp, and a lot of controls and duplicates. It was a tricky panel, and nobody who published got it right. So I sort of became the big debunker of non-A/non-B agents, the infamous "Alter panel." And we couldn't break it ourselves.

But what we did in those years, then, was, while we're trying to develop a test, we had to do other things to help improve the safety of the blood supply. We tried to clinically characterize what non-A/non-B hepatitis was. A lot of people thought it might have been just a transaminitis, just an elevation that's not clinically important. But working with Dr. Hoofnagle and Dr. Debuchele [sp.] and people in the NIDDK [National Institute of Diabetes & Digestive & Kidney Diseases], we started to biopsy these patients, and showed that about 20 percent of them had cirrhosis. So this was not a benign disease, and they could get worse over time.

I think one of the things that I did that was maybe most important in those years was to keep non-A/non-B alive as a clinical entity. And once you showed there was cirrhosis, then people started to get interested in it. Meanwhile, lots of labs were trying to develop a test.

From a transfusion standpoint, around 1981, the rates were ... In the 1970s, the hepatitis rates kind of settled in. They bounced from year to year, but on the average they were probably about 8 or 9 percent, so down from the big 30 percent, but still not disappearing.

So in 1981, we did a study, a retrospective study, from our stored samples, as did another [lab]. There was one other prospective study of transfusion hepatitis going on in the country called the TTV study, the Transfusion-Transmitted Virus Study. That began, I think, in 1978.

Saul: I've heard of the post-transfusion hepatitis studies that were going on. Was the TTV study the same thing?

Alter: Well, it was the same. It was really the same. It's just that it [the TTV study] was a multi-center collaborative study set up by the Heart & Lung Institute, funded by the Heart & Lung Institute. [It was] a very, very good study, and almost always we [who were doing the post-transfusion hepatitis study at the NIH] found exactly the same thing [as the TTV study]. They found what we found and we found what they found. And those were the two studies. Their study ended in the early, in the mid-1980s or early 1980s, but they had bigger numbers than we did and it was a good study. I think we both sort of simultaneously found that if you looked back in these samples and you checked donor ALT levels, the presumption was that since ALT is what we measure hepatitis by in the recipients, maybe if you checked ALT level in the donors, you could use that as an indirect marker.

So we did a study, and it did show that if you got blood, if at least one unit of blood that you got had an elevated ALT, then you had about a three- to fourfold increased risk of getting hepatitis compared to people who got only ALT-normal blood. But ours was a relatively small study, although it was confirmed by the TTV group as well. And we

knew that if we did ALT testing, we'd be throwing out a lot of donors who had ALT for other reasons: alcohol, medications, things like that. So we didn't want to go into this willy-nilly, and we hadn't yet shown that it would do anything prospectively, in a prospective way. I wanted to set up a controlled prospective study where half the group got ALT-tested blood and the other group got blood just the way we were transfusing it anyway. Dr. Mort Lipsett, who was the head of the Clinical Center then, said, "No, you can't do that. It's not ethical. You've already shown that ALT testing has efficacy, and I don't think you can do it." So we didn't do the controlled study. We just started ALT testing in 1981, as did a few other places in the country, but not many. And we then followed the patients again prospectively, through 1982, 1983, and 1984, and we just couldn't show any impact. ALT testing didn't seem to drop the hepatitis rate. I think it's because most of the people with elevated ALT are not really carrying virus. Some of them were, so it would cut out some cases, but you couldn't show it in the small numbers.

Alter: Then, in the mid-1980s, the TTV group published that anti-core antibody, hepatitis B core antibody, could be a surrogate [marker] for non-A/non-B [hepatitis], and they did the same kind of retrospective thing. They looked at the samples and they found that if a donor was anti-core [hepatitis B core antibody] positive, the recipient was more likely to get non-A/non-B [hepatitis]. So we then did a study in our own population and confirmed it, and so it looked like if you got anti-core [positive blood], you had a three- to fourfold increased risk of getting non-A/non-B [hepatitis].

This made a lot of sense to me in the sense that people who were exposed to [hepatitis] B would also be more likely to be exposed to non-A/non-B [hepatitis] because it would include addicts and perhaps those.... So in 1985-1986, I really spent a lot of time talking to the Red Cross, and other groups, trying to convince them, showing them the data on the anti-core [studies]. Fortunately, another study in Germany also came along and showed the same thing. And while we were struggling over this, HIV came along, and it just totally changed people's attitudes about blood. It was clear that a lot of people had been infected by blood, and blood banks had to do everything possible to prevent transmission of infectious agents.

So AIDS was there, and then the AIDS test came along, so AIDS disappeared from the blood supply very fast, in large measure to Gallo [his discovery] and developing a test very rapidly. And the test was implemented very rapidly once it was developed. But blood banks got heavily criticized for not doing anything before AIDS to use as indirect [testing]... In retrospect, had you used indirect markers for [non-A/non-B] hepatitis, they could have been efficacious for AIDS as well, because it would have ruled out the two main transmitters of HIV, male homosexuals and drug addicts. But that was in retrospect. But given AIDS and given the three studies [by then] of [the effectiveness of] anti-core

[testing], [we were] able to convince the blood bank groups to adapt anti-core antibody [testing]. Then when they looked at it, they said.... Then we found, surprisingly, that there was not very much overlap between anti-core [testing] and ALT [testing]. The people who had elevated ALT were different than the people with anti-core, and they both had about the same predicted efficacy. So they [blood bankers] said, "Well, we can't, then, do one without the other," so in 1987, [they] adopted both ALT and anti-core. And, of course, now we had HTV testing in place also, so we had three surrogates for non-A/non-B hepatitis. And then, for the first time, I could see the rates come down. So we had actually gotten down to about 6 percent in the mid-1980s. [This happened because] people were using less blood. One of the things that happened after AIDS [was that] people stopped using blood. They really were much more judicious in the use of blood. A lot of things were happening at once. But by 1989, our hepatitis rates had dropped to about 4 percent, and still, at that point, we hadn't yet developed a specific test for non-A/non-B [hepatitis]. We were really skeptical whether we ever would. But suddenly we found that Chiron Corporation had been working on a non-A/non-B viral discovery program for about six years. They were using molecular biology. When we did our big push [at the NIH], molecular biology was in its infancy. But they used rather sophisticated, then-sophisticated, cloning techniques and came up with an agent that they said was for hepatitis C virus.

So the very first thing they did was, they wanted to get hold of the Alter panel. They sent me the stuff, because I only knew one side of it. I didn't know the full evidence they had that this might really be the agent, so I was thinking, "well, this might well be like all the others." So I wasn't rushing to do the test, but every minute they were calling to get the results. Finally I broke the panel, and they had pretty much broken the panel. All the negatives were negative, and all the positives were positive except for two acute-phase samples. And that was because they had an antibody test, and these people were still in the viremic phase, without antibody, so ultimately those two people also turned positive.

Alter: This was pretty exciting. Then we went back and we looked at all our non-A/non-B cases, all those we had good samples on, and 88 percent of the non-A/non-B cases seroconverted for C. We weren't doing molecular testing. We were just looking for antibody. But we had serial samples, so if they were going to get it, we could show 88 percent seroconverted for C, which was the first real proof that [hepatitis] C [virus] was the cause of non-A/non-B. Maybe it didn't account for every case, but it accounted for most of them.

Then CDC did studies of people who had community-acquired hepatitis, and they found, I think, [that] 80 percent were C related. Then it was all there. [Hepatitis] C testing was licensed in 1990, so very rapidly it got licensed and implemented. I think by 1992, our continuing prospective study showed that hepatitis rates had fallen down to 1 [or] 2

percent, and none of those cases were C. I forget now. Maybe one of them was C. It's in that chart. (*Reference the chart from the Nature Medicine article.*)

And then by 1992, Dr. Curran [of the CDC] came up with a more sensitive test for C, and we never saw another case of C after that. And by 1997, we actually hit zero incidents of hepatitis.

Now, that doesn't mean it's really zero, but within the confines of our small studies [at the NIH] it was zero. And the rates were so low that one had to go into mathematical calculations to figure out what the risk might be. Right now, now that we're screening donors with molecular tests, nucleic acid tests for C, the rate is predicted to be one in 2 million. So if you get transfused now, you have about a one-in-2-million chance of getting hepatitis C compared to a one-in-three chance when we started the post-transfusion hepatitis studies.

Saul: The one-in-three chance wasn't for random cases. It was for the heart surgery patients.

Alter: Yes. It was for people who were multiply transfused, getting paid blood, or part paid blood. It was the highest-risk group.

Saul: And how does that compare to the risk for HIV today?

Alter: The risk for HIV is about the same, about one in 2 million.

Saul: I'd like to ask you to come back to the earlier post-transfusion hepatitis studies that you were working with. One can assume that the objective of the studies was to see how we could prevent hepatitis from being transmitted to recipients of blood. But one could also project that the handlers of the blood samples would also essentially be at risk for contracting the virus. Was that a concern at all at the beginning?

Alter: We weren't really that concerned. I mean, clearly, if you got a needle stick, it was possible. I'd say not so much in the blood-bank setting, but among staff in the wards.

[START OF INTERVIEW WITH ALTER AND ESTEBAN]

Saul: All right. So this is Dr. Juan Esteban?

Esteban: Right.

Saul: E-s-t-e-b-a-n?

Esteban: Exactly.

Saul: And you used to work with Dr. Alter as his fellow. Is that correct?

Esteban: Yeah. I was one of the first fellows that he had here at the Blood Bank. I think the first.

Saul: The first? At the Blood Bank?

Alter: Well, the first fellow in my section.

Saul: Okay. And that was?

Alter: _____

Saul: The first and only.

Alter: Several people from his lab after that.

Esteban: That was between 1984 and 1986.

Saul: Okay. So you were here right when AIDS was...

Esteban: Exactly. I came here almost with AIDS, and Harvey reminded me that that was kind of a coincidence. The virus was discovered when I came here. I had nothing to do with it.

Saul: Right, right, right. Did you work on AIDS at all?

Esteban: Yes, I did. I was involved in studying the samples, stored samples from Dr. Alters' follow-up studies. I actually handled those samples and tested them for anti-HIV.

Saul: Okay, okay. And this was still part of the prospective heart transplant or open-heart surgery study?

Esteban: Yeah. Those were samples from the open-heart surgeries.

Saul: Okay. And so, in addition to the studies for hepatitis in the 60s, these were still continuing on with anti...

Esteban: Well, those were stored samples, and at that time, because AIDS had been recently discovered, and the first kits for testing anti-HIV antibodies became available, he designed the study to try to define transmission through blood.

Alter: I'm sorry. I think...the AIDS... This is good because he really did the key studies.

Saul: Sure

Alter: And mostly the chimp study ____ transmitted HIV.

Saul: _____transmitted.

Alter: Yeah. It didn't prove to be as valuable as the HCD _____ non-A/non-B.

Saul: Sure.

Alter: But the studies of the Western blot_____.

Saul: Yeah. So if you could maybe describe some of the studies that you were working on.

Esteban: Basically, the first study was that retrospective testing of anti-HIV transmission by studying, by using, I think it was Litton Bionetics anti-HIV test that was under development in both donor and recipient_____. looking for sero-conversion for infection in transfused patients from Dr. Alter's prospective open-heart-surgery patients. Sure. And how many did you find?

Esteban: I_____ There were two out of... I don't remember.

Alter: What was this?

Esteban: How many we found with HIV infection. It was two ...

Alter: Among the donors or on the heart patients?

Saul: Among the heart patients.

Esteban: It was two out of...

Alter: We had really basically two collections because we collected all the people who had open-heart surgery, only... It seemed like a lot, but it was only a small proportion_____hepatitis. So in the years after 1970, 90 percent of the samples we had were people who didn't get hepatitis. But those donors and recipients were good to look for other things. So, when you start, the 1980s were mostly people who had been collected in those studies, but they didn't have hepatitis, and very few of them did have HIV.

Esteban: Yeah. Two or four out of...

Saul: Thousands probably.

Esteban: Thousands, yeah.

Saul: So it was really something that wasn't being seen a whole lot of, even with the tests.

Esteban: It was not, because at that time they were already testing for both ALT and HCV, I'm sorry, anti-core of HBB, and that probably decreased...

Alter: We didn't start anti-core until [around] 1987.

Esteban: Oh, really?

Alter: Yeah. We started ALT in [around]1981. We did the studies of anti-core in the years when we were here, but we didn't actually have it implemented as a screening procedure until the rest of the country did in the mid 1970s. But we also were, from [around] 1985 on, we were testing blood donors.

Saul: Right.

Alter: And then we started to detect donors with a positive, so we set up another study that we called NARC, which stood for different things, but it was basically NIH ARC. It was also NIH Retroviral Antibody Consortium or something like that. So we — that study is still going, in fact. We enrolled 284 people, I think, who were HIV positive, 184, sorry, who were HIV positive. Most of them came from the Red Cross. And starting in [around] 1990, we did the same thing for HCV-positive people, and we're now following about___ almost 800 total people in that study, and Juan set up the same studies... I mean, he_____

Esteban: With the controls, we have infected patients about 460 or something like that, plus 120 controls.

Alter: How many___infected?

Esteban: Four hundred sixty.

Alter: Yeah. So we're about_____

Saul: And that's for HCV or that's ...

Esteban: For HCV.

Saul: HCV.

Esteban: Yeah.

Alter: But the concept of a new test comes along, and suddenly you're going to be having to tell donors something, and you don't know what it means, you know, false positives. So we set up both these studies to help clarify how many people are true positives, how many false positives. If they're true positives, what does it

mean? In the HIV study, it meant___we kept following these people_____ as well for a while, but, actually, they were dying off until HAART therapy came along. And now_____

Saul: Until what therapy?

Alter: HAART. HAART is Highly Active Anti-Retroviral Therapy, and that's changed the whole thing for AIDS.

Esteban: It is actually a combination of different anti-retrovirals, the different _____factor.

Saul: Right. So, one of the things I'm interested in looking at was, how did people deal with samples in the lab that were potentially very infectious? I mean, with AIDS, that was potentially more of a concern than even of hepatitis because of... Well, in the early 1980s, it wasn't known how contagious it was or what the morbidity-mortality was. But once you got here in [around] 1984, how did---what kinds of safety precautions were in place?

Esteban: Well, the universal safety precautions that were widely used at that time, the using of gloves, the disposable gloves to handle the samples; avoiding capping or recapping needles; _____. There was already _____ preventive measures for universal safety precautions that were advised by the CDC probably before the HIV epidemic, to prevent HPB infection. Am I right?

Saul: Mm-hmm.

Saul: And what did you personally do? Or was it just not a concern that these were blood samples and you were using them in the lab?

Esteban: Well, actually, my job was retrieving the samples from the facility that you had in Rockville, which was actually — I think that retrieving of the samples was the most dangerous part, because at that time the vials were glass-made vials, and many of them were stuck on the boxes and broke up when you tried to pull the samples. We didn't get any, I mean, we were careful because we knew we were handling potentially infectious material. But that was not more dangerous, actually, than testing the samples, because in the testing lab, all the setup. But we didn't know that we were, would have breaking of the glass tubes. I don't know. You're not using those gloves? You still...

Alter: We are using still some very thick-walled glass tube that's supposedly indestructible, but mostly_____. He's right. They used to freeze and stick to the bottom and break_____. I don't know if you know, but we had a blood bank

technologist who broke a — a tube broke in her hand, and I think she was wearing gloves, but it went through, and she developed HIV and ultimately died.

Saul: Yeah. I had heard that.

Esteban: Oh, really?

Alter: This was not in our section___in the main blood bank

Saul: Oh, really?

Alter: Yeah. And Jackie actually broke a pipette in 19 ...

Esteban: Seventies?

Alter: ____?

Esteban: That was well before I came, because she told me.

Alter: ____[Or] maybe it was in the 1960s.

Esteban: Or maybe the 1960s.

Alter: I think it was the late 1960s, and got hepatitis B, and for six years had pretty severe hepatitis B .

Saul: ____ Who was the person who died of AIDS?

Alter: ____.

Saul: But mostly plastic now in terms of...

Esteban: Yeah. At the time of testing, everything was____there was no one who had the vials____ was only opening with the gloves on, they were careful, and the pipette tips were plastic made, so ____ was actually not high. ____ myself__higher risk when I went back to Spain, because I remember sticking myself with a plasmapheresis needle. I wanted to get rid of the needle, and instead of using a safety container, a hard, plastic safety container, I used a soft plastic saline kind of____and actually I broke through and got stuck with the needle. And it was____ acute type infection____ And for three months I was very scared.

Saul: Yeah, I can imagine.

Esteban: But then nothing happened.

Alter: ____.

Esteban: Huh?

Alter: ___In one of our patients in the NAARC study, and___pinprick sensations and he had a neuropathy. And I don't know why, ___ I think I was recapping the needle and___.

Esteban: Which you should not have done.

Alter: Right. But I was thinking it wasn't even a blood sample___a pinprick test, and I stuck myself, and then looked, and there he is bleeding from___pinprick test___seem like a leper, you know, kind of ___washed my hands_____But I went on anti-retrovirals___.

Esteban: That was already when they were giving anti-retroviral therapy for a month.

Alter: Yeah, for a month. It was horrible___And___ a lot of empathy for patients who took the 14-15 pills a day.

Saul: Yeah. The prophylactic treatment___.

Saul: It must have changed as well. Do you still give gamma globulins for hepatitis exposures?

Alter: For B you do, but not for — we don't have one for C.

Saul: Okay. So there's no prophylaxis for hepatitis C. Got it.

Alter: _____Somebody gets stuck with C, you wait until they became RNA positive, and then the question is, do you treat them then or do you let them naturally recover and treat them six months later, and there's controversy about that. Most doctors wanted to treat it___, but I would wait six months.

Saul: Oh, would you?

Alter: Again, the treatment is not easy.

Saul: Right.

Alter: I say that now.. But they've done some of those studies in Spain

Saul: Oh, really?

Esteban: We treated acute hepatitis, a post-transfusion hepatitis patient before testing for HPV was available, so we had to rely on ALT normalization to ensure recovery. But because of the small number of patients___and the lack of a non-A test, at

that time the difference between those who were treated and those who were not treated was not statistically significant. It was barely significant___.

Alter: Were you using interferon alone?

Esteban: Interferon alone, yes. And for three months.

Alter: Because interferons weren't as good then, either, as they are now.

Saul: Right. My stepfather had hepatitis C and went through the whole treatment process, and he was not happy for a long time.

Alter: ___Very hard___.

Saul: Right. So during the time you were here, there were universal precautions in place, and you were probably the one who was in the most danger from picking up the samples. That is just great. But you never...

Esteban: I never got any problem, no.

Saul: With hepatitis or with...

Esteban: Or with HIV, because I was involved also in the AIDS study and the blood-donor AIDS study and were drawing samples, but I was using small butterfly needles and using gloves every time, changing, washing hands, and...

Saul: And since you did — the first study you told me about was the ...

Esteban: The first study was the retrospective evaluation of___anti-HCV transmission between blood donors and recipients. And the second one was a follow-up of the HIV-infected blood donors.

Saul: Okay.

Esteban: One of them.

Alter: Didn't you do the Western blot___?

Esteban: No. That was probably____.

Saul: Anything else in terms of...

Esteban: The NIH is the safest place in the world because they keep telling you in almost every place, if you think you may be pregnant, don't get close to that thing because it gets radiation. When you go to the bathroom, they remind you to wash your hands. So I think that... And usually the risk comes from when you're not,

you don't care enough about those measures and you don't follow strictly the rules, like he said, recapping the needle. Sometimes you think it's helpful...