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Interview conducted by: Stephen Pemberton, M.A., 1998 Pisano Fellow of the Stetten Museum and NIH Historical Office (*transcribed personally on August 5-6, 1998)*

Abstract: Opening introduction and remarks omitted. I explained to Dr. Alter that I was interested in his hepatitis work, and asked him to recount his involvement with the Australian antigen discovery, etc.

Harvey Alter: I came here [to the NIH] as a blood bank fellow, and was looking for the cause of transfusion reactions unrelated to the known reactions against red cells, white cells and platelets . I had set up a system to use agar gel plates to determine if blood recipients had antibodies against proteins in blood donors or other healthy subjects. The concept was that when a transfused patient was exposed to a protein in donor blood that was different from their own, they might develop an antibody to that protein and that this antibody-protein interaction might be visible by the formation of a precipitin line in agar One day, Dr. Richard Aster, a now famous hematologist and platelet expert, who was working in the blood bank at the time, said: "I just heard this interesting lecture by Dr. Baruch Blumberg and he's basically using the same technique you are to search for inherited differences in serum proteins. The next day, I went over to talk to Blumberg and we immediately set up collaboration. Blumberg was a geneticist, and he was looking for inherited differences in serum proteins called polymorphisms. Using a similar method to my own, he set up agar plates, by the method of Ouchterlony, and used serum from a patient who had been transfused in the middle well of a 7-well template and reacted that in each pattern against 6 sera arrayed around the periphery of the agar gel pattern. These sera were derived from normal individuals that Blumberg had collected from diverse populations and geographic regions around the world. Using this relatively simple technology, Blumberg determined that there were different kinds of genetically determined beta-lipoproteins in human serum. One of the characteristics of beta-lipoprotein precipitin lines in agar was that if you used a stain for lipid, the line turned blue. Secondarily, we would counter-stain, with azocarmine, . a general protein stain, that stained the precipitin line red. One day, I observed a precipitin line that didn't stain blue, but counter-stained brightly red. Thus, it appeared more to be a protein than a lipoprotein. It turned out that the sera reacting in the agar were from a hemophiliac, who had been multiply transfused, and an Australian aborigine. This novel antigen was first called the red antigen, but ultimately was termed the Australia antigen for the aborigine from which it was derived. We then looked at other aborigines, and the antigen was very prevalent in that population, approximating ten per cent. As an historical side light, we first called it the red antigen, because it was red rather than the expected blue line characteristic of the

beta lipoprotein polymorphism. Subsequently, we debated whether to call it the Bethesda antigen for the place where it was found or the Australian antigen for the origin of the patient. In those days, they were naming hemoglobins for the place the patient came from, so we elected to call it the Australian antigen (*Au*). The name did not seem such a big deal at that time because its clinical significance was unknown.

The next step was to look for this antigen in patients and normal donors. We found that about one in a thousand donors (0.1%) were *Au* positive. Then in testing various NIH patient populations, we found that about ten per cent of patients with leukemia were *Au* positive whereas the antigen was rare in other disease states. Hence, the first paper describing this new antigen, emphasized the association with leukemia. We postulated that the Australia antigen might somehow be related to a leukemia virus. There's a whole other story about how *Au* became recognized as A E hepatitis virus, which I wasn't involved with, but which Blumberg pursued with dogged persistence. His perseverance taught me a great lesson for my subsequent research. Initially, Blumberg and I were both at NIH, but in 1964-65, Blumberg moved to the Institute for Cancer Research in Philadelphia and I went to U. Washington in Seattle to complete my medical residency.

The Australia antigen story then went through a series of serendipitous events. In fact, at one point, a writer commissioned by the Library of Medicine wrote a monograph on serendipitous events in medicine, and used this hepatitis story as the main focus. At the time of discovery, we essentially had an antigen of unknown significance. Blumberg, because he was a geneticist, thought this was an inherited antigen and because it seemed to be associated with leukemia, he tested persons who had an inherited predisposition to leukemia, namely patients with Down's Syndrome. As seeming conformation of the leukemia hypothesis, these Down's patients had a very high prevalence of the Australian antigen. Much to Blumberg's credit, he did not accept this as confirmation that the antigen was directly related to leukemia and hence he looked at Down's syndrome patients who lived in different environments. Those living in large institutions had an *Au* prevalence of about 33%, whereas those who lived in small institutions had a prevalence of 10%, and those who lived at home and newborns had a prevalence near zero. This suggested that it wasn't really Down's syndrome that was the critical component, but rather the environmental setting. This was the first clue that *Au* might have an infectious etiology. By chance, a technologist in the Blumberg lab who had always served as the *Au*-negative control suddenly turned *Au*-positive coincident with her developing symptoms and lab results consistent with viral hepatitis. A similar *Au* seroconversion occurred in a Down's patient with hepatitis. Tom London in the Blumberg lab, then measured liver enzymes in Down's patients who had the antigen versus those that showing an association of the antigen with liver enzyme elevations. Finally they tested patients with acute and chronic hepatitis and showed a strong association between antigenemia and hepatitis. This was a major breakthrough in the history

of hepatitis as it led to the first diagnostic test for any hepatitis agent and ultimately to a hepatitis B vaccine. Around 1969, it also focused attention on the association between this antigen and transfusion transmitted hepatitis and this is when I reentered the field.

I came back to NIH in 1970 to take over prospective studies of patients transfused at the time of open heart surgery. These studies had been initiated by Robert Purcell, Paul Holland and Paul Schmidt. In this study, patient samples were collected before and serially after blood transfusion and tested for ALT, a liver enzyme whose elevation indicated inflammation of the liver. When ALT elevations were noted, we were able to test stored samples and show that a proportion of the patients who had post-transfusion hepatitis became Australian antigen positive during the course of that illness. This is one of several studies that showed *Au* was linked to a transfusion-transmitted agent, the hepatitis B virus (HBV). Soon thereafter, we showed that HBV wasn't the major transfusion-transmitted agent. After the discovery of the hepatitis A virus (HAV) at NIH by Feinstone, Kapikian and Purcell, we were able to show that the non-B agent also was unrelated to hepatitis A, the only other known hepatitis virus at that time. This new agent was given the awkward designation, the non-A, non-B virus (NANBV) which more than a decade later was cloned and renamed the hepatitis C virus (HCV).

Nonetheless, because of this association, by 1970, we were in a position to start testing donors routinely. This led to the first test for a hepatitis virus and had a big impact on hemophiliacs, on everybody, but on the hemophiliacs in particular because most of the clotting factor pools that they received were contaminated with HBV. And it was becoming clear in those years that hepatitis was really devastating to the hemophilia population because the better their treatments got, the less these patients died of bleeding, and the more they were susceptible to blood-transmitted infections. Prior to universal hepatitis B virus testing, a lot of hemophiliacs contracted and later died of hepatitis B. Lou Aledort and others started performing liver biopsies on these patients , and showed that many of them had chronic liver disease; hepatitis became the leading cause of death in hemophiliacs in the '70s and '80s, before AIDS devastated this population.

By 1970, the Australian antigen was re-designated the hepatitis B surface antigen (HBsAg) and by 1971 this test was mandated for all blood products in the US and Europe. It was very effective in cleaning up the clotting factors administered to hemophiliacs and in markedly reducing the transmission of HBV through routine blood transfusion. As noted above, once we had a good test for hepatitis B, and subsequently for hepatitis A, we show that most of the hepatitis transmitted by blood and blood products was unrelated to either of these agents and designated as non-A, non-B (NANB) hepatitis. We had no test for the NANB agent and could only diagnose it by exclusion of A and B. That was where things stood through the '70s and then in the early '80s, HIV/AIDS came along and dominated the infectious disease landscape.

Nonetheless, in the early 80's, we looked at whether transaminase (ALT) testing of donors might prevent some transmission of NANB hepatitis. In a retrospective analysis of our donor-recipient data, it looked like there was a three-fold risk of getting NANB hepatitis if a patient got a unit of blood from a donor with elevated ALT. Thus, we implemented ALT testing in 1981, but as we continued to follow these transfusion recipients, we couldn't show an impact of ALT testing and such donor testing was subsequently abandoned. Then around 1984, the Transfusion-Transmitted Virus Study group (TTVS), funded by the Heart-Lung Institute (NHLBI) showed an association between anti-core antibody and NANB hepatitis. We were able to confirm that in our stored samples: our data showed that if one received an anti-core positive unit, there was a three- to four-fold increased risk of developing NANB hepatitis. We thought it might also serve as a surrogate marker for HIV and a direct marker for HBV. Hence, I became a strong advocate for universal anti-hepatitis B core testing which was then implemented in the US in 1987.

At the heart of many lawsuits in hemophilia litigation were based on the question "Why wasn't anti-core donor screening introduced earlier?" Such testing would invoke significant donor loss and the consensus was that the data needed to be unequivocal. Eventually, there were three studies, the TTVS study, our study, and a German study, that were all in the same direction and it was felt that these combined data were sufficient for the FDA to mandate universal donor screening. A major problem was that the anti-core test had no confirmatory test and the majority of the tests proved to be false-positives. Since 1987, we have lost one to one and half per cent of our blood donors based on anti-core testing, many of which were false positives. So introduction of this test was going to have a major impact on the blood supply and we didn't want to do it frivolously. As stated the test was introduced in 1987, but hemophilia advocacy groups felt strongly that it should have been introduced earlier. However, sufficient data really weren't available until about '84 and implementation prior to the AIDS outbreak would have taken a prescience we did not have.

Inactivation of clotting factor concentrates was a more logical solution to preventing HIV, HBV and HCV transmission to hemophiliacs, However, initially it appeared that the inactivation of viruses would also inactivate the clotting factors in the product. Eventually, industry developed technologies that could destroy viruses while retaining clotting factor potency e From that point forward, the virus hemophiliac population has received the safest blood of any population because all Factor VIII concentrates have been virus-inactivated. At the same time, the whole blood supply has become much safer through a variety of interventions and as we've continued to follow patients prospectively, we have shown that the rate of transfusion-transmitted hepatitis, which was about 30% in the 1960s, and had fallen to about 10% in the '80s, is now down to virtual zero. It isn't quite to zero, but the current incidence is probably around 0.1%. The change over 4 decades has been dramatic.

SP: Dr. Hoofnagle said that you hadn't seen a case of transfusion-related hepatitis in a while.

HA: We have looked since 1992, and we've had only one case of unclassifiable hepatitis and no hepatitis B or C cases. We picked '92 because that was when the second generation hepatitis C test was licensed and implemented nationally. It has been highly effective and transfusion-associated hepatitis is on its way to becoming an historical relic.

SP: Let me back-track for a moment and pick up on some of the things you have mentioned. You are in what division?

HA: I am in the Department of Transfusion Medicine in the Warren Grant Magnuson Clinical Center. The Clinical Center is the hospital that serves all the NIH Institutes.

SP: Now you mentioned the TTV group out of the Heart, Lung, and Blood Institute.

HA: TTV is actually an outside group of investigators that was supported by the NHLBI. It's not on campus.

SP: So it's an extramural program.

HA: Right.

SP: What was the time frame for that work?

HA: It was in the late ‘70s and early 80’s. Pretty much, we were the only two places that had ongoing prospective studies. You have to do these things prospectively because most viral hepatitis is virtually silent in the early stages. You can't wait for people to come and tell you, "I've got symptoms." The two prospective studies were the NIH study and the TTV study. Earlier there had been prospective studies performed by the VA and the US Army. The TTV study ended in the early ‘80’s, but we've continued our study.

SP: Where was that study located?

HA: It was in multiple centers. The coordinating unit was in Los Angeles and others were in Houston, St. Louis, and New York. It was a bigger study than ours and very well done. But the beauty of our study is its longevity and our ability to document a markedly declining hepatitis incidence over time, namely from 30% prior to 1970 to near zero by 1997. Of the 30% prior to 1970, we found retrospectively that only one-quarter was due to HBV. In 1973, a sensitive donor screening test for B was commercialized and the subsequent incidence of transfusion-associated B hepatitis dropped to virtual zero. In '75, the hepatitis A

virus (HAV) was identified by Feinstone, Kapikian and Purcell at NIH and an antibody assay developed. When we applied that test to our non-B hepatitis cases, we showed that none were related to HAV. Thus, the majority of cases were classified as non-A, non-B. Much later, it was shown that almost all NANB cases were due to the by then cloned hepatitis C virus.

SP: What accounted for the marked drop in hepatitis incidence in 1970??

HA: The reason the rates of hepatitis were so high prior to 1970 were threefold. First, the heart-lung machines used at that time required a lot of blood for priming and hence most patients received 10 or more units of blood at the time of surgery. Second, our study was prospective and depended on biochemical evidence of hepatitis and not clinical evidence. Thus, we were able to detect asymptomatic cases that although initially mild could nonetheless progress to severe outcomes such as cirrhosis. Third, about half our blood supply came from commercial establishments that paid their donors. Studies at NIH and elsewhere showed that such donors were very high risk. In 1970, we adopted an all-volunteer blood donor system and introduced the first generation tests for HBV. This resulted in a precipitous 70% reduction in TAH. The big drop was both in B and in NANB because these paid-donors were transmitting both agents. The B test helped, but adopting an all- volunteer donor base was really the main thing.

By 1971, the whole country went to a volunteer system -- except the plasma centers. Plasma centers continued to pay for blood and utilize large donor pools for manufacture of derivatives. Hence, blood plasma and its derivatives remained high risk until efficacious inactivation procedures were introduced almost a decade later.

SP: Dr. Hoofnagle mentioned something that he thought was amusing. He thought, it was his contention, he attributed this to Dr. Schulman, that the Australian antigen should have been called hemophilia antigen. From his perspective, he was saying that it was awfully difficult to get serum, and he felt I guess looking from the outside that the hemophilia serum was integral to what Dr. Blumberg was doing in that discovery. I'm not necessarily writing about this, but I was wondering what your reaction to that kind of statement would be.

HA: Oh my. I usually agree with Jay, but I don't buy that. Just using a hemophiliac patient because they were multiply transfused and thus might develop antibodies to serum proteins different than their own does not constitute grounds for saying they were essential for this discovery. We could have used any multiply transfused person. What it should have been called was the Bethesda antigen because then it would have been clear that the discovery occurred at NIH. Once Blumberg left NIH, he kind of forgot that the discovery was made here. Everything was said to be coming from Philadelphia. However, all the subsequent findings linking *Au* to hepatitis did come from Blumberg's group in Philadelphia and they deserve full credit for that. Another thing is that Blumberg thought this

was an antigen for all hepatitis agents, but the late Fred Prince at New York Blood Center showed that it was specific for the serum hepatitis virus, namely HBV. So I don't think it should have been called the hemophilia antigen. It was the aborigine who had the hepatitis B antigen in his blood.

SP: I didn't think you would.

HA: Hemophiliacs because they were exposed to so many donors in large plasma pools unfortunately became an experiment in nature for viral hepatitis.

SP: After Dr. Hoofnagle brought that up, I told him that I was interested in writing a chapter about what hemophiliac's themselves label themselves -- as "canaries in the coalmine". That type of story fits rather nicely within the confines of a larger narrative about how hemophiliacs have often been at the center of breakthroughs and discoveries that have little to do, necessarily, with their primary disease, but that have generated a lot of good work in fields other than hemophilia research proper. And very seldom does that stuff come back to impact.

HA: I don't know about that. First of all, the problem with calling them "canaries" is that canaries are brought into the mine knowing that if something is there they may die. Nobody knew these things were a risk to the hemophiliac. It happened that they got it. There's something intentional in the canary analogy that I don't think is valid. They feel that they were guinea pigs, but they also needed to be treated for their hemophilia. In fact, when the issue came up "do you want to receive cryoprecipitate?" which was a single donor product and not the high risk pooled donor commercial product, it is my understanding that most patients with hemophilia opted for the commercial product because it was easy to administer, could be kept in a home refrigerator, could be used prophylactically or at the time of a bleed and essentially because it changed their life. Of, course, this was before the advent of HIV/AIDS that changed all transfusion paradigms.

SP: Doesn't cryo involve some pooling?

HA: Cryo, well, you can pool it. But if you do, it's small pools. It is made as individual units, and then you can pool them afterwards.

SP: Right.

HA: I'm not unsympathetic with the plight and tragedy that befell the hemophiliac population. They got multiply exposed to all the major agents, HIV, HBV and HCV, before adequate testing and inactivation procedures were in place. It was a tragedy, but they weren't guinea pigs, and they weren't canaries. It was only after the fact, that it was realized they were getting these highly contaminated blood products. Now, could things have been done sooner? That's debatable. We couldn't have tested sooner. We didn't have the technology. We might have been able to do core testing earlier, which would have helped some, but not prevented

everything.

SP: When was the core antibody developed?

HA: Well the test was available since the early 70's, but solid evidence that it could be used as a surrogate for other agents was not published till the 80's as noted above. Actually, Dr. Hoofnagle was the first to suggest such use of the core antibody test. Had there been a good core test, with high specificity and a confirmatory assay, where one could just exclude the real core positives, it probably would have been implemented earlier. As it was, it excluded 1-2% of the donor population, when only perhaps 0.1% were truly infected.

SP: I realize that a lot of this is contentious. I don't particularly have a view at this point, but there is a lot of talk about the extent to which a lot of these problems could have been prevented. Just based on what I know, it doesn't seem likely. Dr. Hoofnagle was saying a little about this. I asked him what he thought about efforts within industry to approach any of these problems. He said that they weren't typically R & D types.

HA: One of things I think was a problem was that NANB wasn't recognized initially as a serious disease. One of the things that I am proud of, our NIH group kept NANB alive because we kept showing that the frequency of its occurrence and then accumulated evidence of its potential severity. But it was frustrating not to be able to identify the agent visually or by culture and not to have a test for it. Investigators kept dropping out of the field. It didn't have an impact like AIDS that drew investigators to the field. Had it come along with obvious, serious complications, I think industry would have worked harder to develop tests and to develop inactivation technologies. It was astounding when it was finally shown that you could heat material and still retain potent Factor VIII activity. Early on that seemed unlikely.

SP: The prevailing opinion that Factor VIII and other clotting factors were vulnerable to heat, that persisted for how long, do you think?

HA: Well, certainly, I think through the advent of HIV. Through the '70s for sure and even through '82 or '83. I was not privy to what the companies were doing, but at some point they found you could lyophilize Factor VIII and then heat it and still retain coagulation activity. Better mechanisms of inactivation came along later. Mostly, it was all driven by the dire need to prevent HIV transmission.

SP: You knew Dr. Shulman?

HA: Yes.

SP: Could you tell me a little bit about his work?

HA: I'm not sure how Dr. Shulman initially got into the hepatitis field except that he was a coagulation expert and treated patients with hemophilia. He was also an expert in platelet disorders, especially idiopathic thrombocytopenia. He had developed complement fixation and hemagglutination assays for measuring anti-platelet antibodies. Girish Vyas at UCSF, who was into hepatitis and knew Shulman initiated a collaboration with Shulman and they developed a method to screen for hepatitis B by hemagglutination. That, I believe is how Shulman entered the hepatitis field. I understand that in the early days of HBV discovery, there were some contentious times about nomenclature of the hepatitis B virus. Apparently, at a meeting in Yale which I did not attend, Blumberg, Prince, Shulman, and Paul Holland, got into some rows into what the Australian antigen was, what it meant, and what it should be called. But I think Shulman's involvement was mostly from the point of that test, and he did some nice epidemiology using that hemagglutination assay. But then, he sort of dropped out of the field. He didn't have any impact on the field beyond that. I don't think he was really into treating hemophiliacs in terms of their liver disease. So he did some wonderful work on platelets. That was really the strength of his work.

SP: I haven't talked to the clotting people yet. But I'm trying to find out what was taking place on this campus in several different areas with coagulation studies or anything related to plasma fractions or concentrates.

HA: You know, the group that was working here at the time was with the FDA. Lou Barker, Bob Garrity, Ed Tabor, John Finlayson and David Anderson were studying where viruses fractionate, something vital to their responsibility in regulating blood products. So they would be worth talking to and the rest of the work was being done by Bob Purcell on a more basic virological level. Bob and I were collaborating on the clinical and transfusion aspects of hepatitis virus infection. Bob was my primary mentor throughout my NIH career and he contributed significantly to the discovery and elucidation of every hepatitis virus from A to E. Jay Hoofnagle started at the FDA, but then came to the NIDDK Liver Service.

The nice thing about the NIH is its highly collaborative nature. We've all worked closely together, particularly Purcell's group and our group and Hoofnagle's group. And Shulman was never quite in that setup because his interests weren't into hepatitis much after '75 or so.

SP: One of the things that I am interested in from around the mid-'70s up until '82 or '83, getting a pretty good sense for what the issues were in the treatment setting, about what kinds of issues were preoccupying hemophilia specialists. Obviously, people like Dr. Aledort and others are key types of people to talk to for that kind of thing, but in terms of hepatitis issues, what were the central concerns of the time. You've described better, sensitive tests, bringing down transmission rates. Do you have any thoughts beyond that?

HA: I was working more from the standpoint of whole blood transfusion. We would make a change and then see how that change affected hepatitis incidence in our prospective study. As noted above, the big change was going to the all-volunteer system in 1970. The secondary impactful event was introducing routine hepatitis B surface antigen testing. Then, we didn't have anything new to offer until finally in '81 we added ALT testing. We didn't add anti-core testing at NIH until 1986 and even then, it was hard to show that it had an impact. However, the combination of HIV testing in '85 anti-core testing in '86 and more intensive and direct donor questions that by 1989 saw hepatitis rates fall to 4.1% in our prospective study. Then in '90, the first test for hepatitis C came along. And that dropped C rates by about a half. By that time, our total hepatitis was down to about 2%. In '92, the second generation test for C came along, and dropped rates to near zero. That's where we are now….virtual zero. The hemophiliacs meanwhile got down to zero at some earlier point because of inactivation as well as testing.

If we had been more advanced in inactivation technologies and had introduced anti-core testing when AIDS came along in '81, there would have already been mechanisms in place to prevent it HIV transmission by blood. But these measures were not there in time.

SP: Regardless of that question, in general, when a new test becomes available, and you're trying to evaluate it and promote it to the broader blood banking community, what's your general impression of how that works?

HA: It was not easy to introduce a new test early on. As litigations increased, it got easier and easier. By 1990, when hepatitis C came along, it went in very fast. It was a very specific test for a virus. When you talk about indirect tests, with a lot of donor loss, it is hard to introduce those things. It took probably a year and a half to convince everybody to do core testing. Then you've got to go through the FDA.

SP: You said you were particularly proud of keeping the NANB issue alive through the '70s.

HA: Then pushing for core testing in '85 or '86.

SP: What do you think were the resistances, say in the '70s, to NANB.

HA: First of all, it was a mild disease. It wasn't recognized that bad outcomes could come; or if they did, they were rare. And that's true. It is mostly a mild disease it doesn't cause much of an acute illness. The extent of the chronic disease wasn't recognized until later. Some of the best studies came from close follow-up of patients with hemophilia. Surprisingly, they were able to perform liver biopsies in these patients after coverage with clotting factor concentrates. Among others, these were done by Joel Spero at U. Pittsburgh and then Lou Aledort at Mount

Sinai in New York. Aledort put together a compendium of biopsy results in an influential paper published in Blood that showed a lot of chronic liver disease in patients with hemophilia. Prior to this, there was reluctance to biopsy hemophiliacs because of the major risk of bleeding. The main impediments to advancing the field earlier was the failure to recognize the long-term severity of chronic NANH hepatitis and the lack of a specific test for the causative agent. We tried everything we could think of in the 70's and early 80's without success. It must be remembered that molecular biology was just emerging in the 80's and this was what was needed for HCV discovery. It took Chiron six years of intensive labor to finally clone the agent. Abbott Labs was looking for it all along without success. Indeed, investigators throughout the developed world, were looking for the NANB agent it, but they began to give up after repeated failure. The truth was, it would have never been found by the serologic methods we were using. Viral antigens just wasn't there in sufficient quantity and it took time for molecular biology to evolve. Dr. Hoofnagle spoke a lot about the importance of the radioimmunoassay. I guess in the early '70s.

SP: That centered around what he was up to at the FDA. Is it your sense that when a more sensitive assay comes along or a more reliable one what's the status under which an assay like that becomes clearly more reliable? He talked for a while, and I think he confused me a bit, about it being difficult initially to get people to switch over to using radioimmunoassays. Particularly, he said, some of the fractionators were using it, and he characterized them as the more responsible, good ones and there were some in the industry who weren't, and it wasn't clear to him who was using it and who wasn't. Eventually everybody in the industry got on board. Have you had similar sorts of things.

HA: I'm not sure. First of all, one of the groups that deserves a lot of credit in all this is Abbott Labs, in particular, that really advanced the technology. We started testing in 1970 with agar gel diffusion, and pretty soon there was counter-electrophresis, which was the second generation test for B, and that came in '71. In '73, I believe, the very sensitive radioimmunoassay was commercialized. It was developed in a relatively short time. This was used for blood donor testing until enzyme immunoassay became the preferred test because they were easier, safer and because no radiation was required, and still very sensitive. I thought the plasma industry followed the same test progression as blood banks, but I don't really know.

SP: How would you characterize the plasma industry of the '70s versus the plasma industry of the '80s after HIV crisis was more or less recognized?

HA: Well, I've always been against the use of paying donors. I think they were using donors of known high-risk. It wasn't so clear what the risks were, but a lot of their donors were alcoholics and probably shooting up. In terms of albumin, it didn't matter because that product got pasteurized. Gamma-globulin seemed to be safe just by virtue of fractionation. So the risks fell on the Factor VIII, fibrinogen

and other clotting factors. The early treatments for hemophiliacs consisted of only fresh-frozen plasma and then cryoprecipitate so it didn't involve the plasma industry. I don't know the year that commercial clotting factor concentrates were first used. It was being marketed in the late '60s.

HA: Concentrates?

SP: Yes, concentrates. The first one came out of Hyland, Los Angeles. It was jointly developed between Chapel Hill and there. I know a little bit about that. By '70, I think you had two or three products coming out.

HA: They were using donors that we wouldn't use in the whole blood situation, and a significant proportion of these donors were carriers of HBV and HCV and later of HIV. These products were very high risk until viral inactivation procedures were put in place.

*End of tape and formal interview*

Off tape Nothing significant was said. Dr. Alter suggested that I risked getting him in trouble with the industry. I told him that they already had too much trouble to handle. We spoke a couple of minutes more about the blood supply situation. He mentioned that we forgot to talk about his work with chimpanzees. He then presented me with copies of the monograph he mentioned, a report on hepatitis, and his CV.