

Dr. David Aronson

November 22, 2002

This is an interview with Dr. David Aronson in Bethesda, Maryland, on November 22, 2002.

The interviewer is Jessie Saul.

Saul: We're talking today with Dr. David Aronson, and Dr. Aronson has been at the FDA and, previous to that, the Bureau of Biologic Standards.

Aronson: The Division of Biologic Standards.

Saul: The Division of Biologic Standards, for quite some time.

And we're going to talk today about safety practices in blood banking and how the NIH has been involved in producing blood-supply safety policies and your experiences with NIH in general, which is quite a wealth of experience.

If I could ask you first about, we've been talking a little bit about sort of blood issues in general, and I wondered how you ended up at the NIH to begin with.

Aronson: Well, in those days, there was a doctor draft.

Saul: A doctor draft.

Aronson: This was in 1956. After I finished my internship, I became what became known as the yellow berets, a stint in the Public Health Service. For the first year, actually, I worked down with an epidemiology group downtown

under Dr. Carol Palmer, one of the big gurus in tuberculosis epidemiology.

But the laboratory work was more my interest, and I found a position out here in the old Division of Biologic Standards headed up by Dr. Roderick Murray. And life was good in Bethesda, and to get out of the Public Health involved filling out too many forms, so I stayed in for 30 years.

Saul: Because there were too many forms to fill out.

Aronson: Yeah. And then when the work involved too many forms to fill out, I resigned.

Saul: Okay. (Laughs)

What kinds of projects were you working on when you first got here?

Aronson: The plasma proteins in general. I sort of fished around for the first year or so, working mostly on plasma protein, coagulant prothrombin, and the biochemistry of that, which was just beginning to be understood.

There were very few regulatory issues in those days. The first regulatory products we had were the some of the very early fibrinolytics, including streptokinase, plasmin, and plasminogen, but things like purified factor 8 for treatment of hemophilia A were on the horizon. Fibrinogen was a little bit of an issue. That's not back that far. I think those were the things I remember off of the top of my head. There must have been a couple of others.

Saul: Sure. Getting into that kind of product-related research, what kinds of

safety factors were on the horizon at that point in time?

Aronson: The issues always were hepatitis at that time. Hepatitis had been described after blood transfusion in the early '40s.

Saul: Okay. You had mentioned before that we should go back to the '40s to really understand blood safety at the time.

Aronson: Yeah. And that goes back to the birth of blood banking and transfusion. In the early '40s, during the Second World War, was when they started appreciating that this was an issue. People turned yellow. You did not have accurate and precise tests for hepatitis in those days. What you had was a measurement of serum bilirubin or the patient getting jaundice, which, when they turned yellow, that was, you had a case of hepatitis. And it was hepatitis, one thing. And the pattern was sort of similar, and most people got better. Occasionally you would have somebody who didn't get better, and this was usually in an older age group. But it was considered an acceptable risk.

Saul: By who?

Aronson: By the public health community. If you read the literature in the mid-'40s, blood transfusion was considered one of the great therapeutic advances of the century, which was young then. And things like people with bleeding ulcers could be saved, when they used to die.

Saul: Right.

Aronson: So that was an acceptable risk.

What they didn't know was the degree of the risk. When I arrived at NIH, the open-heart surgery was just starting, and another member of DBS at the time, Joe O'Malley, was interested in hepatitis.

Saul: Who was that?

Aronson: Joe O'Malley, Dr. Joe O'Malley, and was working on isolating the virus. And _____ samples, and he talked to the surgeons at the Clinical Center, and they said, "We never see hepatitis." When finally they did this study -- I think it's the late '60s; it must have been about the late '60s -- they found something like 30 percent of the patients were getting hepatitis.

Saul: Now, who said they never see hepatitis?

Aronson: This was Dr. -- I think his name was Dr. Moore, the chest surgeon, who used to use a lot of blood. These were 20 units just to prime the pumps in those days.

Saul: Sure. This was _____ who ended up doing the heart study in the post-transfusion hepatitis study.

Aronson: Well, he may have been on it, but . . . And Paul Schmidt at the blood bank, they didn't get any feedback on it. Occasionally there was a, one patient who finally, I think, got them interested in this -- it may have been in the mid-'60s -- who . . . And they said, "We never see it," because the patients were removed from the hospital. The surgeons, of course, never saw that, and the patients were all from out of town, somewhere else. But there was one patient who did come in. He was a professor of

biochemistry, if my memory serves me right, at a small college in Ohio
You can check those facts with John Finlayson over in Building 29. But
anyway, and he died, again if my memory is correct.

But that stirred up a little bit of interest because now, as you were
getting into more pooled blood products, and just the baseline hepatitis
risk became apparent with the biochemical tests you had available. Instead
of just, what was it, the . . . There was bilirubin and there was something
called the -- the test depended on sort of abnormal precipitation of some
protein, which were very imprecise. The Keflen [sp.] flocculation test.
And these were the tests . . . Then in the mid-'50s, you developed
biochemical tests that measured very specific enzymes, which are still in
the laboratory testing used today. But you had no way of chasing down
the virus. The only model you had was using human volunteers.

Now, Dr. Murray did that for a while and used mostly volunteers in
prison, which will get everybody upset these days. But it was well done
and honestly done and with all ethical considerations taken care of by
most. There weren't three-page written things and nobody knew what was
going to happen.

Now, these were done during the war. You actually had people
who didn't want to go in the army. There's a word for it.

Saul: Conscientious objectors.

Aronson: Conscientious objectors who would volunteer for this and other studies

that were done, as well as prisoner volunteers.

Dr. Murray did several very important studies on viral inactivation at that point, showing that if you heated plasma for 10 hours at 60 degrees or plasma fractions for 10 hours at 60 degrees, you did not get hepatitis.

Saul: Just to clarify, we switched from talking about blood to talking about plasma and the different studies that were going on. The post-transfusion hepatitis studies with cardiac surgery patients -- that was with whole blood.

Aronson: Yes.

Saul: Okay. And the plasma, there was a similar concern for plasma?

Aronson: Yes.

Saul: And how, what . . .

Aronson: This, because of the known hepatitis risk in blood transfusion, it was assumed that that would transfer to plasma, that the infectious agent would be in plasma as well in the blood cells. In fact it was more in plasma than in the blood cells, probably. So when plasma fractionation began under Dr. Cohen during the war, this was immediately realized as an issue. They assumed that it would be an issue, but they didn't have any data, obviously.

Saul: This was back in the 1940s.

Aronson: This is 1940-1945. But, incidentally, they found a way to, in one case, to make the fraction albumen viral-free. This was not the intent. The intent

was to produce a product, which, in the vernacular of the old protein laboratory in Boston, would be stable in a tank in Tobruk, Tobruk being a small city in the north of the Sahara desert and under very hot conditions, and they found that there was a stabilizer, caprillic acid, that could be added, and it made it stable to high temperatures, and they tested this for 10 hours at 60 degrees. And later studies of Dr. Murray and other people of protein showed that albumen heated at 60 degrees for 10 hours did not transmit hepatitis. This was important to point out. This was liquid plasma, not dried plasma.

Saul: Why is it important to point out?

Aronson: Because viruses are inactivated at lower temperatures in liquid state than in dry state.

Saul: Oh, okay.

Aronson: So that worked.

The other plasma fractions that were being produced, fibrinogen and human thrombin, which was considered useful for stopping hemorrhage, were quickly found out to cause hepatitis, and the thrombin problem was fixed by making a bovine product which was free of hepatitis and, at that time, any known transmissible disease.

The fibrinogen was considered an important product, although there is no clinical data to this date that shows that.

Saul: What was it considered to be important for?

Aronson: Again, for stopping bleeding.

And one of the more interesting things was that the immunoglobulins, the antibodies from the plasma in a separate fraction, rarely produced any infectious disease. The Protein Foundation in Boston tried various methods to inactivate viruses, including a chemical beta-propiolactone and ultraviolet light, common. These were tried out, but you didn't have good clinical data, and eventually it was quite clear that the way they were being used was not sufficient to inactivate viruses. So they pretty much fell by the wayside in this country, although a company in Germany used that up until, oh, maybe 15 years ago.

Saul: Do you know what company that was?

Aronson: I can't remember their name offhand.

Saul: It wasn't Immuno, was it?

Aronson: No, no.

Now, that leaves . . . I mean, the real holding point here was, after Dr. Murray's experience, nobody wanted to give test products in humans.

Saul: Dr. Murray being . . .

Aronson: Being Ron Murray, who was head of DBS, had done the early work with the Protein Foundation on injecting samples into volunteers, and when he had a volunteer die, he decided this was not something to do. So, in essence, there was no way of getting around this. You either had the product with a risk or you had no product. This became very clear in the

case of the hemophilia.

Now, the first product for use in hemophilia A patients in this country was licensed, I believe, in 1962 or 1963. It was a product made in the same way as you made fibrinogen, and you knew that it contained hepatitis.

A colleague who worked with Dr. Brinkhouse [sp.] in those days down in Chapel Hill was the big guru in hemophilia -- we didn't even have the word guru in those days -- talked about a meeting they had in the late '50s with a young biochemist, Murray Seelin [sp.], who was working on the purification of factor 8, and the issue of hepatitis came up. And Dr. Brinkhouse [sp.] looked up and said, "Our patients are dying of hemophilia. They're not dying of hepatitis." Now, the options in those days were plasma for any patient with hemophilia A, or we didn't know the difference between hemophilia A and hemophilia B for most of that time. It was to be treated with plasma transfusion or to be treated with nothing.

Now, to treat a severe hemophilia A with plasma would take a minimum of 500 units a year, and this was pushing the envelope for how much you could give to a patient.

Saul: How big is a unit?

Aronson: A unit is about 210 mls. A patient who had -- severe hemophilics who bleed 25 times a year, you want to treat them, so you give them the most

you can give over 24 hours might be four units, four or five units, I guess, in a young, healthy guy, and you could raise the level up to about 20 percent of normal. But that level only stayed raised for about half a day to a day. It was not satisfactory treatment. These patients were in the hospital for months at a time. At that point, with plasma therapy, median age at death had gone up to about 30 years. Before plasma therapy was available, it was said to be about 15 years. I don't know how solid that data is, but that's . . . So there was a big advantage to having a pooled plasma fraction for the treatment of the patient with hemophilia. Instead of infusing two liters of plasma, you could get the same effect with 100 to 200 mls of the concentrate, and you could get much more efficacious treatment of the hemorrhage. So you were between a rock and a hard place in terms of transmissible diseases.

Saul: Because, was it known that . . . Not all of the products were infected with hepatitis. Or were they?

Aronson: You began to get the feeling that in fact -- and looking back, it was clear that every lot was infected with hepatitis, 100 percent of them.

Saul: Okay. And was that known before, when _____?

Aronson: No, no. And this was not detectable. And in fact this wasn't detectable by any test. And you treated the patients, and you had no test for whether they had hepatitis B other than they turned yellow. I'm not kidding. This is basically it. Now, most patients who got hepatitis didn't turn yellow.

How many? What is it? You can check with Harvey Alter. He'll know. Five percent get jaundice within six weeks to six months, depending on the dose and the type of hepatitis. So these kids who got it young were okay because the problem . . . Well, let's see how to jump at it.

Let's stay with hepatitis right now. We're thinking of one virus, although J. Garrett Allen [sp.] at Stanford said, because there seemed to be two incubation periods, there seems to be one a little bit shorter, more like six to eight weeks, and another one more like three to six months, and that was the only data you had about the chance of a different hepatitis virus.

It was quickly realized that the blood-transfusion hepatitis was not the common hepatitis, what we now call hepatitis A, because different epidemiology, shorter incubation time, etc. So the . . .

Now, what did I want to split? Hepatitis B and hepatitis C. Hepatitis B was associated with more of the acute death, or so they thought at the time. And, again, all this stuff on hepatitis, Harvey can give you the real answer. But hepatitis C, when it was first described in the early '70s -- I think the publications are about 1975 -- was considered almost benign. Yes, you had occasional rises and sporadic rises for a long period in people of certain liver enzymes associated with hepatitis, but in general they looked healthy. So this was -- the hemophilia treaters considered this, well, it's just a transaminitis. It really doesn't mean . . . Our patients are doing very well. Whereas, and hepatitis B is our big

concern. So that was your big effort in terms of improving viral safety. I mean, it's presumptuous of me to speak on hepatitis B testing with Harvey coming in, so maybe I . . .

When the hepatitis B tests came, they were implemented as soon as possible. We're going right through the whole, initially with the amino precipitation methods, counter electrophoresis. Ray Shulman [sp.] at the Arthritis Institute -- I think that's where the Hematology Branch -- had a complement fixation test. As soon as he became available, they were used, and the big trial was done by Martin Goldfield in New Jersey, which just blew your mind out. He got rid of essentially all fatalities from acute hepatitis, although there were still -- and 50 percent of people came down with clinical hepatitis, which we now realize is hepatitis C. But that was a breakthrough. Immediately, all the plasma fractionators started screening with and updated as the test came along. This was a no-brainer; there was simply no reason not to do it, and it was effective and everybody was happier.

This test really improved the blood-bank safety. The impact on the plasma products I think was significant. There was one study done by -- I think Hal Casper [sp.] was probably on that paper, and another, the Hemophilia Center at Los Angeles Children's Hospital, where they followed young patients who'd only been treated with factor 8 derived from screened plasma, and they found a low percentage of patients with

antibodies to hepatitis B.

Now, what this indicated, it wasn't foolproof, but before you had that screening, it would have been 100 percent. There was -- you'd get one or two lots, and because of the pooled product, you didn't dilute enough to prevent disease. You ended up with, everybody had to be exposed. So that was a great leap forward.

Now, you had a test for hepatitis B. Now you had people getting interested in developing other models, and development of the chimp hepatitis B model was -- a lot of that was done between sort of the triangular, between Harvey Alter, people in Building 29, Lou Barker [sp.], and Bob Purcell in Building 5, infectious disease. So you developed -- in the early '70s, you developed an animal model for hepatitis B using chimpanzees. You got their sensitivity, how long it lasted, how to test for it. You couldn't use -- turning yellow wasn't a good sign. They did have their drawbacks. There weren't that many of them. You had people who said that was not nice to use chimpanzees for that. In fact, it worked very well, and a tremendous amount of knowledge came out of that that allowed the development of the hepatitis B vaccine. So hepatitis B . . .

Saul: Quick question. I'm sorry. The chimp colony here was -- did that help get around the problem of not wanting to test in humans?

Aronson: Yes.

Saul: And that was for heated products, or was that _____.

Aronson: That was for both. First you developed the model of how sensitive they were. Then they were a primary tool in deciding whether inactivation methods were successful or not.

Saul: Okay.

Aronson: So they were a crude tool. A clinical trial of one chimp is not . . . But they really -- it was very important that this happened, because starting in 1975, we had a model to test viral inactivation. And there were a couple of things tried in Building 29, in Biologics, that didn't work, but at least we had the tools to test them.

Saul: What were those things?

Aronson: The chimps.

Saul: Yeah, but what was tested?

Aronson: Well, one was immune removal of hepatitis B by using a hepatitis B antibody column. We had good tests by 1975 for hepatitis B. Antibody you could get from donors with a high titer. One of them was me. And then you made, you bound this to a support and then you run your plasma through, and you then put the plasma that's been through that column into a chimp.

Did an experiment on that, and two out of three were fine, but the third experiment said there breakthrough. It would not be sufficiently good for therapeutic, but it was a start.

There were some other things tried.

Then -- I ought to get off. Well, I can't get off Harvey's subject.

In 19 . . . Okay. Once hepatitis C became known, the same progression went for hepatitis C. So by 1980, you had a chimp model for both hepatitis B and hepatitis C. And by . . .

Okay. Now, that lays out the groundwork. Those were important steps. Those were very important steps. You'd identified hepatitis C and hepatitis B. You didn't have a hepatitis C blood test, though. That was more difficult. But you could get started on viral inactivation, and the manufacturers, most of the manufacturers, I think, started working on viral inactivation, even before that time.

Everybody _____. Everybody had an idea what might work, and it always fell on its face, like the beta-propiolactone and the ultraviolet light. You had this problem of treating it, treating your plasma or plasma fraction or whole blood with some conditions that would selectively kill virus but leave the biological activity alive.

You still have that argument -- it's not an argument -- going on today with whole blood, because a lot of the crucial elements being used for treatment now are the cellular elements, and these you cannot treat the way you do the plasma protein, so there was a meeting on that several months ago. So our focus was on the easier part, the plasma proteins.

Saul: And the plasma proteins are easier because there wasn't the red cell . . .

Aronson: There weren't the cellular, and I don't know whether it's preferable to go

through sort of a time sequence.

The first breakthrough -- and this . . . The particular aim here, at this point, had always been the hemophilia population. It really was -- this was the high-risk group. They're 100 percent; you don't get much higher than that. So you had some, you had a lot of characterization of hepatitis B, you had had a little characterization of hepatitis C, but you did have an animal model. And there were some ways you could say, okay, this is hepatitis C and not hepatitis B. Even though he has hepatitis B antibodies, this is probably caused by . . .

The same other big thing coming out in 1980 was Harvey Alter's clinical report on follow-up of patients with hepatitis C, saying this is not a benign disease. A significant number of these patients after -- I think the follow-up at that time was 10 to 12 years -- have significant liver disease.

Okay. That's -- the viral inactivation is the next step you're interested in, I'll bet.

Saul: Right. And one thing to think about as well, and then we can go back to there. I'm also interested in the practices inside the laboratory that kept the laboratory technicians and technologists and the scientists safe and how those changed as well.

Aronson: You're young, you're beautiful, and you're immortal, and you accepted a risk, and hepatitis was not a lethal disease. It was annoying, it could make you sick. I think I may have gotten my hepatitis antibody pipetting with a

mouthful of a peanut butter sandwich. But this is . . . You accepted, this was part of life. And, in fact, I developed hepatitis B antibodies as well. I had them as soon as the test became, any test became available. They started testing them, the people in the lab who wanted to be put on routine tests for the whole liver, every three months or six months. I did not see any reason for that. And over the years, Dr. Hoofnagle got his test results back and it said, "You have acute hepatitis," and he stayed home for a couple of days and said, "The hell with it. I'm bored. I'm going back to work. I'll feel better at work than I do at home." And then one of the veterinarians who dealt with blood products and the chimps came down with it, and he was a little sicker. How many people in the lab had antibodies to hepatitis, I don't know. But there were only two that had any clinical symptoms at all that I know of, and Jay wouldn't know what it was unless he'd gotten his liver test just done, and nobody turned yellow. It was not an easy . . .

I've got to admit, once the hepatitis C story started coming out, I got a little nervous, because I'd had a syringe full of a plasma product that was infected, and, you know, every time I went to stick a mouse, the mouse would move and I'd stick myself. I mean, I'd drop the syringe and it would go . . . I mean, right there every time.

And a couple years ago I got a little nervous about this and I got, I sneaked in under the wire and got a test for hepatitis C, and I didn't have it.

And I should have been a prime candidate. But, no, I don't think anybody . . . This is not a big issue in the lab, really.

Saul: It's not now, or it has . . .

Aronson: It was not at that time. Laboratory infections were very rare and usually benign.

Now, having said that, I have to say I got my middle name from a man who got a laboratory yellow fever infection and died of it just before I was born. So, my father worked with tuberculosis his whole life. I grew up on tuberculosis. I was taken to his lab as a kid. I mean, infectious diseases were a part of life.

Saul: Did you consider it a badge of honor to have been infected?

Aronson: No. It was -- you had 50 to 100 every year in high school, at least, and this was a very small high school. At least one or two people would get polio. This was just life. I know several of my classmates had siblings who died of bacterial diseases as infants. And polio was part of life, risk was part of life, and you went on with it.

But the lab knew that -- there were, I think, over in the virology group, I don't think -- with the viruses they were working with, I don't think any, I don't remember anybody coming down . . . A man who'd worked there for a while and then went to a university did get a monkey virus that gave him a bad encephalitis, was not a good outcome. But, yeah, this happened.

But we were the greatest generation and tough, I guess. We did not fear exposure to things and knew that a little exposure gave good antibodies. But we didn't know about hepatitis C or HIV.

Okay. I'm going to get into the viral.

The laboratory safety wasn't an issue. When they built -- is it building, not Building 5. Which building is the Infectious Disease Institute? Eight? No. Ten, 11? Just up the hill from eight. And they built that in about 1950 or '51 and they had, they had put in separate ventilating units for each room or something so that the bacteria wouldn't go from one place to another.

There was a man by the name of Herman DeBree [sp.] there, and I don't believe there's any . . . And he tested it. I think that maybe even the day he contaminated one room with spores from a benign bacteria and then tested the other labs, and they all -- they found this going through all the labs.

Saul: Oh, he did? He found it?

Aronson: Yeah. Well, one of the problems was -- and this was not the only time that was . . . The architects had put the air intakes right next to the air output, or close enough by that . . . I think the same thing happened over at Walter Reed.

Anyway, viral inactivation; you're interested in viral inactivation.

Saul: Sure.

Aronson:

Okay. The problem is to kill the virus and keep alive the proteins you're interested in, and I'm going to focus on the proteins because I don't deal with cells.

Everything _____ was tried. Beta-propiolactone and the UV hadn't worked at doses. It was obvious from other reasons that ionizing radiation like cobalt or x-ray or things like that would not work because you killed the protein before you killed the virus. Nobody had a good idea. You were balking at sort of . . . You knew that at 60 degrees at 10 hours, you could get rid of hepatitis B in solution. But the plasma preparations used for the treatment of hemophilia couldn't stand 10 hours at 60 degrees. They turned into jello in about half an hour or something.

And the initial breakthrough that was interesting in the sense -- this was Boehring [sp.] in Germany. They were trying to further purify the factor 8. By the way, I'm using factor 8 for what I usually call anti-hemophilic factor human in the American parlance, but that's the more international. And that's the part that's deficient in the patients with hemophilia A. So Boehring [sp.] was interested in making more purified factor 8. Most of the protein in the factor 8 preparations was fibrinogen. Fibrinogen is heat-sensitive, so they decided maybe we can heat-precipitate the fibrinogen and still get out the, have the factor 8 be in solution. When they did this, they found, after several years, that if they put in a lot of sugar, that they could heat the preparation enough to kill,

precipitate the fibrinogen and at the same time maintain anti-hemophilic-factor activity. And so that was good. In, you know, a half an hour, and they got rid of this, they got a tenfold more purification. This is good.

And then they got to thinking -- now we're getting towards the late '70s -- they started thinking -- mid- to late '70s -- "Well, maybe we can extend this heating period now that we've stabilized it. Maybe we can extend it enough so that we can pasteurize and kill hepatitis." I didn't know this whole story until I came across a court deposition, because I wanted . . . But in '79, they presented the data at a meeting in London, and they didn't give out . . . [recorder cut off] They prepared it, but, "Look, we've got a preparation. We can give it to chimpanzees, and they don't get hepatitis." That was the first step.

It turned out several other companies were working at that time, but nobody really had a good idea. Cutter Labs in California was working, actually, on a similar method to this and having a lot of trouble.

The problem with the Boehringer [sp.] material was that you, the recovery was extremely bad.

Saul: _____.

Aronson: Out of one liter of plasma, you would get 80 units of AHF, an 8 percent recovery, and you would need about five to 10 liters to treat a single bleed.

Saul: Right.

Aronson: Anyway, Boehringer [sp.] had it, and that, to me, was a stimulus, and it can

be done.

So other companies were working on it. We tried several other little piddling things that didn't work. And . . .

Saul: Was there a big push for this at the time? Whose motivation was it to take that viral-inactivated product?

Aronson: Well, you start going to the people in Blood and Blood Products over in Building 29, all blood. That was a big issue. That was probably the top, the holy grail to us.

Saul: Okay, to get heat-activated . . .

Aronson: Yeah. To the manufacturers, to some of them, this was very important if it could be done, but they didn't see any way to get it done. I . . .

TAPE 1, SIDE B

Aronson: . . . guess there were others with smaller research departments that didn't think about it too much. But it was quite obvious by 1982 that most companies had some sort of work. Most commercial companies, interestingly, had viral-inactivation projects underway. This is in contrast to the national blood centers in Europe. Neither England nor France or any, Sweden, Denmark, had any viral-inactivation procedures under investigation. These are much smaller groups and didn't have the resources that somebody like Boehringer [sp.] or Cutter or Immuno. Now, I don't know when Immuno started on their viral inactivation. Okay. So that was the state.

By, okay, 1982, things got a little bit exciting. One of the interesting shifts there was, in 1982 was when the hepatitis B vaccine was licensed. All of a sudden hepatitis B was much less of an issue than it had been in the past. But we did have procedures being worked on because we had the model system for hepatitis B, which was a little bit better, I think, or better at that time than the hepatitis C.

And there was enough interest in 1982 that I put together a meeting. I wanted to have it in the spring of '82 but couldn't get the people together until, it turned out to be September 5th. I think it was September 5th -- why do I say a date? It was the first week or so in September -- to discuss what Biologics wanted in terms of data for a virally inactivated product.

There was much discussion about one chimp experiment. How much could you use what are now called surrogate viruses, viruses that are related, seem to be very tough viruses? If you kill so many viruses of X virus that you can use quantitatively in the lab, does this give you important knowledge, and is that a useful procedure for licensing a viral? And the basic overview at that time from Biologics was that, to be able to label your stuff as viral inactivated, you'd better have data saying you substantially removed, significantly removed a virus of importance to the patient. Well, there were only two at that time, hepatitis B and, well, HIV had just come up on the radar screen. That's a new term since I was a kid,

too.

So HIV, we didn't know anything at that time. You didn't know what it was, but you'd had the first report from CDC of the six -- I think six, no, three -- three hemophilics. I always enjoyed that first -- I think it was the first line in that MMWR: Three hemophilics with no chronic disease. Anyways . . .

Saul: Notwithstanding the fact that hemophilia is a chronic disease.

Aronson: Yeah.

So, anyways . . .

Saul: This meeting about Biologics and what they wanted for viral inactivation, that was with manufacturers who would be presenting _____?

Aronson: That was -- I got into trouble for that one. Maybe I shouldn't put this on the record. At that time, all meetings at FDA were supposed to be public and must have, be published in the *Federal Register*. Well, this was an important working meeting, and there's no way you wanted 53 or 100 people who didn't know the viral, the details of the viral and viral-inactivated . . . You wanted, you wanted mostly the companies who were directly involved. I also did not invite any of the companies who were not licensed in the United States. This was our issue, and we had decided. It was, I think, a helpful meeting, and . . .

Saul: Extra people would just ask too many questions or not understand? What was the concern?

Aronson:

Well, you're in a class of 30 people or 100 people. Where do things go better? You have a committee meeting with 10 people or 40 people. Which goes . . . This was a very hard-working committee meeting with a lot of different, the views of people very knowledgeable. I mean, among the manufacturers, we had, Harvey Alter was there, Bob Purcell. Was Lou Barker still . . . Yeah. Lou Barker was still there. So we had a lot of knowledge there. If you used _____ virus, which ones were good? Bob Purcell discussed the heat-inactivation differences between the duck hepatitis and the opossum hepatitis or whatever they are, and, I mean, it was that kind of meeting.

But we came away saying, okay, the one-chimp model or a three-chimp model is what we're going to have to have. I don't think we decided the numbers. Then we got into a problem with chimps in short supply. Some of the manufacturers seemed to have some. I tried to . . . Well, that meeting at least got us set in a frame of mind, we knew what we wanted, at least at that time. And that came up again at an advisory committee meeting I think in November or early December. It must have been early December. And we laid down the law and said, "You need hepatitis B inactivation studies in chimps." Basically, the next day we sort of changed that. I think it was after that meeting that we sort of changed it. Send us the data before your . . .

The chimp study takes a long time. It's six months minimum, six

months and all the laboratory testing, so you're talking nine months. So send us the data, and we'll start reviewing it even if it doesn't have chimp data.

Saul: Okay.

Aronson: But the other point that was coming up was, with the hepatitis B vaccine, was the hepatitis C story, so we sort of dropped our primary goals being hepatitis B inactivation and said hepatitis C. And the results from the first studies looked very good for hepatitis C, or reasonably good. You were screening out a lot of bad donors for other reasons by this time. It looked okay, and the heat inactivation looked good. We had no idea about hepatitis C biology at this point.

So we licensed between '82 -- our first license for a viral-inactivated product was for the Baxter, and that was licensed in March of 1983. It was either February or March. Dennis Dunning [sp.], who was then the director of the Laboratory of, the director of Blood and Blood Products, apologized to me. I'd signed off on the license, I think, December 11th or something around there, and Dennis apologized to me at the end of January. He says, "With all these AIDS meetings, I haven't been able to get to that license application you signed off," which, in retrospect, I think was ironic.

Well, immediately after that was licensed, the Italians set up a trial with people who'd not been treated previously, a term that's now known in

the trade as PUPs, previously untreated patients. The PUPs were treated by either the heat-inactivated stuff of Baxter or another product, and they were followed for hepatitis. And guess what? They all came down with hepatitis. Well, this is over a course of a year. This is an important year. He started that probably in late '83 and had results in late '84.

Saul: Okay.

Aronson: And by late '84, well, all the patients, heated or unheated, came down with hepatitis. But by '84, you had tests. You'd identified the virus and you had antibody tests for it.

Saul: For?

Aronson: For . . . Sorry. By the mid- and end of '84, you had tests for HIV, what we now . . . We didn't have that same name for it. I forget what we called it then. You had tests for HIV virus that was doable and could be done, and you tested those patients, and Dr. Menucci's [sp.] trial for HIV, the ones who got the heated stuff did not get HIV and the ones who got the unheated stuff did.

Male: _____ change the tape?

Aronson: Yeah.

Male: Take a break?

Saul: Would you like a glass of water or anything?

Aronson: What I'd really like to do is go to the smoking room, but you don't have those anymore.

Saul: Unfortunately, no.

Aronson: I'm glad you said unfortunately. See, we took all sorts of risks.

As a kid, my father and I would put asbestos in the pipes in the basement. We were upper-middle -- we were middle class. We had asbestos on the pipes, we had lead paint, high-class lead paint in the house. We put mercury in our teeth.

Saul: All kinds of stuff.

Male: This tape has one more hour. Do you think it's _____?

Aronson: That's more than she can take.

Male: Okay. _____.

Aronson: Okay. I have the Italian story. This is an important story in all the history.

So the heated patients and the untreated patients came down with hepatitis. The definition by that time -- this was presumably almost all hepatitis C. But these patients who'd received the heated stuff did not come -- in the interim, tests for HIV had been developed. The patients in the trial who received the heated stuff did not get HIV. And, boom, the world changed. This was the first time that hooked up the animal model . . . Well, it dissociated the animal model for hepatitis from the HIV. I'd gotten hell in the '83-'84: You shouldn't have licensed that heat-treated stuff; it's junk. You . . . At a DBDR meeting here, the advisory council to NHLBI on blood products, I was taken over the coals: You needed a clinical trial. Well, I felt better after that.

And then out of CDC came some very good data saying that HIV was a very sensitive agent, and, in fact, all the licensed products killed a lot of HIV, obviously some more than others. But that was a . . . But what is fascinating to me, if Dr. Menucci [sp.] had done that Italian trial a year earlier, look what would have happened. People would have said, "This is not a useful viral-inactivation technique. It shouldn't be on the market. Take it off. We won't use it," and we would not have, they would not have revisited that in the light of HIV.

Saul: So that was the first trial?

Aronson: That was the first clinical trial.

Saul: For the heat-treated . . .

Aronson: Yeah, yeah. And that came out just about the time data from CDC saying that HIV was heat labile, more so than, obviously, than hepatitis B.

So that is interesting to me because people keep saying, "Well, why didn't you do this before? Why didn't you do this before?" Well, we didn't have animal models; we didn't have the models for either B or C until later on. When we had those, we developed the method, which did work on HIV but didn't work, even though the chimps liked it, it didn't . . . A weird sequence of events. Sometimes you guess and you're right. So I think our view was, even if it's not perfect, it's doing something.

I think, again, the hepatitis inactivation had been a focus for really, in blood, for many years, and we were more aware of it than either the

patients or the treaters.

Saul: More aware of the heat ____.

Aronson: Of the issue. We wanted -- that was a major issue to us, more so than the . . . Both the regulators and the manufacturers I think were more interested in this than the users, which is, you listen to the rhetoric now, it's quite different. I don't think that was true then. I know it wasn't; I know it wasn't.

Saul: There just wasn't a demand for it.

Aronson: No. Oh, until May of 1985, we allowed both heated and unheated on the market, and then enough of this stuff. But I received -- there were abstracts. I received phone . . . Ed Gompert [sp.], who was running the hemophilia center at Children's Hospital in L.A. at that time, called up and said, "My patients don't think that the heated stuff works as well as the unheated stuff." I don't know where that sense got built into this. Well, this was just at the time when we were deciding that . . . I said, "Don't do that trial, Ed, because we're going to stop it, all this unheated stuff."

Saul: When did -- well, did you ever actually outlaw unheated product?

Aronson: Yes, as of May 29th or 30th of 1985. We did not have a withdraw. That becomes a big issue with lawyers.

Saul: Right.

Aronson: Did not have a withdraw because you wouldn't have had enough stuff on the market for at least six months.

Saul: So you would have been shortchanging the patients. They wouldn't have had product at all.

Aronson: They wouldn't have had product.

The second thing, the tragic thing to remember, is by June of 1985, essentially everybody who was going to be infected had been infected, except the newborns. But this becomes a big issue and a legal issue. Did you withdraw things? And the answer was no. As you improved, you didn't withdraw.

In March of 1983, changes in donor screening were mandated. Should we have withdrawn things that were, had withdrawn before? Well, that would have made a six-month gap there. Six months later, there were other changes. And this went on down the line for years. When a given lot, when a given donor was clearly implicated, then we would withdraw the lots where that donor was known to have . . . But that was about all that could be done.

The American Association of Blood Banks set up a meeting about six years ago asking the question, "If another virus like HIV comes along, how can we anticipate it?" Now, (a) the very good virologists there, we had no idea there was a virus like AIDS, like HIV. And after a day of discussion, Neal Nathanson [sp.], Bob Shope [sp.], Harvey Alter was there. We can't. Here's a virus which has a long incubation period and has no visible signs. I always wondered why we only found hepatitis.

Because people turned yellow.

And this comes up again because of the issue on West Nile. I had occasion somewhere in the '83 to call the CDC's expert on arboviruses. I forget his name. He was out in Fort Collins, Colorado, and I finally got him on the phone and said, "I'm not a virologist, but we're finding new things. Viruses other than those that turn you yellow are involved in transfusion issues, and should we be worried about arboviruses?" I mean, these are a common and varied group. And he almost laughed me off the phone; he almost laughed me off the phone. I said, "Okay, sorry to bother you." And so then I read about West Nile, and the next test we've got to have is a West Nile, a test for West Nile arbovirus. It's not the issue that HIV was or hepatitis B. But funny things happen. But I don't think West Nile virus is a big issue, I've got to admit. Where do we stop?

I just read an article by Michael Bush. You know the name?

Saul: Mm-hmm.

Aronson: Okay. He was speaking -- I think it was written with Harvey -- on the nucleic acid testing, if you did individuals versus pooled, and the cost. I mean, there is a limit.

Now, in the FDA, you didn't have to think of the economics except as taxpayers and health insurance payers. But we were focused on safety. But even there, you had to -- there's a risk-benefit. You inject something, the risk is not zero. The patients who think they should have zero risk, it

doesn't happen.

Saul: Do you think that's changed, the expectation for zero risk? Has that changed over the last 10, 20 years? I mean . . .

Aronson: Oh, yeah. Well, people want zero risk as opposed to the view before. Oh, hepatitis, we'll get it, and that's that. But it's a societal change now. It's a societal change. And, yes, a young child dying is a tragedy, but paying \$100 billion for somebody not to die . . . What was it? I think the figure Mike Bush gave for saving one person from a hepatitis C infection was \$20 million or \$20 billion or one infected unit.

It's not political to discuss these things. But my biggest risk in life was not working in the lab. It's to walk to work and cross Old Georgetown Road. I'm not kidding. Three times I've been carried on hoods of cars into the middle of Old Georgetown Road as a pedestrian. I've been lucky. Most of us, 99.999999 percent of us are very lucky. Zero risk I don't think comes.

Saul: Can you describe for me, the issue of zero risk for patients who receive these products is something that's come about more recently. What about the issue of risk for people who work in labs? That's very different now than it was when you first started working. And can you trace who made the changes in that attitude shift and sort of what . . .

Aronson: It hasn't been an attitude shift, I think, of most of the people who work in labs. I think for the vocal groups, it has been. I mean, I worked in a lab. I

worked in Building 29 from '58 to '87. I then moved downtown to George Washington and worked in a lab there for 10 years. Now, by the time I left . . . Now, when John Petricciani [sp.] gave me a tube of HIV, which had just been described, with a dose of nominally 10^{-8} per mil, we didn't have P1, 2 or 3 facilities. I did use it under a hood and I did wear gloves, and maybe even wore a mask. I doubt that. No, I couldn't. I did not pipette it by mouth. There were certain things . . . Most of the pipetting I did in Building 30 was by mouth.

Saul: Through what time period?

Aronson: From 1958 to 1987. I was exposed. I was bathing in plasma. What it had, I was going to get. That didn't bother me. I rarely wore gloves. Occasionally . . . With a known infectious sample, I would wear gloves. With a standard sample, no, because it was cumbersome, you couldn't . . . So then you'd pick up a pen to write and you've got stuff . . . I mean, it didn't make sense to me. Now I'm over at the Clinical Center and I work in a lab there, and I look around and make sure nobody is watching and I pipette by mouth because I'm used to this.

Now, I don't think the people in the lab really care that much, but the spokesmen feel they have to. If you have a committee meeting, the most conservative person wins the day. And I don't think that the people are that worried.

Saul: The people working in the lab?

Aronson:

We were wallowing in HIV before . . . You know, HIV didn't start in '82; it was probably around since '75 or even before that.

Lab risk, yeah. There are different kinds of labs. There are certain things I wouldn't work with or I'd work very carefully with. But with standard patient samples . . . The needle stick issue is, yeah, I didn't like to stick myself with a needle, but most of the time it wasn't because I threw away, I reached in the waste and . . . It was because I dropped the thing. When we disposed stuff, we tended to bend the needles to keep people from getting stuck. We autoclaved all our infectious material right in the lab and then threw it in the regular trash. There were chemical issues I think that were probably more than the infectious-disease issues there. There were a couple steps we did that we didn't have a hood for and we did without a hood that probably would have been better under the hood. But did we worry about lab safety?

Well, there was one issue. Yeah. We had moved from Building 8 to Building 29 in July of 1960, I think it was. And in Building 8 there was a routine. You checked the laboratory showers, the hazardous-material showers, every couple of months because they'd get filled with rust. And somebody will hold a washbasin under the shower and we'd pull the shower and often we'd unscrew the head and dump out the rust.

Got over to Building 29, brand-new building. You know, after a year, you know, "Over in 8 we always had problems. Let's -- we'd better

check the showers." Well, we had a big, tall, broad-boned girl from Kansas, Genevieve. I had been trying to think of that name for a couple days. Genevieve Nash. "Genevieve, you're tall. Can you hold this under the shower, and I'll pull the chain?" She says, "Sure." I pulled the chain, the shower comes out, I let go of the chain, and it doesn't stop. And Genevieve _____ what's happened. The water's rising in the room.

Saul: Oh no!

Aronson: Finally it stopped. It was on a controlled -- it had to release at least 50 gallons.

Saul: Oh, my God!

Aronson: These newfangled things. So we were concerned that the safety showers, we were aware of where the fire extinguishers were in the lab. They were by the door, but if we got trapped in the back of the lab, we couldn't reach them. Those I think were almost more of issues that . . . I don't remember anybody worrying about getting an infectious side effect. I think we were more at risk for the chemicals. Then they came out with you should wear gloves when you use acrylamide. Well, we didn't wear gloves with acrylamide, and the only person who came down with acrylamide-associated illness, a guy who used it a lot and kept gloves on, but the acrylamide got in under his glove and he was exposed to it all day long. So it's a crap shoot.

The laboratory? I don't see this as an issue at all.

Saul: What about the OSHA regulations for lab workers who deal with blood and infectious materials?

Aronson: I remember going to a meeting where we heard spokespeople say, oh, we've got to do this and that, and mostly I thought it was nothing that was helpful or would improve safety. These were often union representatives. I don't know what OSHA lab regs are. A lot of regs I don't know and most other people know. Does OSHA say I can't pipette by mouth?

Saul: Yes.

Aronson: Why does it say I can't pipette by mouth on benign buffers?

Saul: I don't know.

Aronson: I know more than OSHA about pipetting and do more than anybody who wrote those regulations. Yes, I've pipetted sodium hydroxide into my mouth and I'm aware of the damage there. As I say, the chemical hazards are . . . But I don't see any . . . Yeah, you can make mistakes. But there are a lot of points. I pipette better and more efficiently by mouth than I do with bulbs and things like that. Now, if I grew up with them, maybe it would be different. If somebody new came in the lab, I'd say, "Okay, do it this way, but here's the way we used to do it."

Saul: Sure. What has been the relationship -- I'm moving more into the policy issues here -- what has been the relationship between the FDA and the NIH, the blood bank particularly, since they were the ones dealing with a lot of the blood _____?

Aronson: Well, first off, originally the Clinical Center blood bank was under Biologics. You knew that.

Saul: Yes.

Aronson: Oh, you know more than I do. I don't think there was ever any formal arrangement. Certainly, I mean, the triumvirate for the viral diseases was always there. Purcell, blood banks, and Harvey and our group was always there. Most of my contact with the blood bank was to carry their plasma over to Building 29, which I wouldn't have been allowed to do without getting a material-transfer form. I can't get a little bit of plasma _____ without . . . I mean, I think the world is not going better in some ways.

Boy, we had a lot of _____ in terms of policy. No. I mean, policy issues are kind of easy. We want to make things safer. That was -- I don't think we . . . I can't ever remember sitting down and discussing blood-bank issues, policy issues.

Saul: What about, where did you get -- did you bring in expert advice from other places when you would, for FDA regulations?

Aronson: We had a very good . . . In 1975, the first time we had an advisory committee that was appointed, about '75, it was really the best people in the country, and that keeps up till today, just as DBDR had their own advisory committee. Now, we would sit in on those meetings, too, and there would be more policy issues come up there than I think in our day-to-day contact with the blood bank. But, yes, we had an extremely good

initial group, really, with a consumer advocate, Lou Alladord [sp.]. And there was always _____. It's grown a little bit and gotten a little too politically correct, I think. But . . .

Saul: What do you mean by too politically correct?

Aronson: Well, you can't . . . All blood bankers have a conflict of interest. Therefore, you can't have a blood banker on your advisory board. And Mike Bish [sp.] was on there and they fired him, and they fired a lot of . . . So there's very few people who know that much about the blood banking. Many more consumer representatives, some of them whom were very helpful, and some of them were just a pain in the butt.

But the advisory committee, a very interesting phenomenon there. It's a real social phenomenon. The advisory committee meetings were always open and announced ahead of time, and you would have a fair number of people come in. You might have, oh, 80 people come in to listen to the advisory committee. Most of these were manufacturers, but there'd be other issues you'd have people come in for, to hear what was going on. And there was a lot of free and open discussion between everybody in the room.

Since I've left, it's become much more formalized. And before the meeting, the FDA outlines its questions, and then you take a vote, whereas previously it was more of a consensus development and more of a policy rather than a regulation meeting, and it was very useful, at least for me it

was.

Saul: Why were they useful?

Aronson: (A) you meet some very good people who have a lot of knowledge. It was useful -- a different kind of knowledge than I ever had. These were people you could pick up the phone in those days and call them up and say, "Look, you said this at the meeting, and you know this. But we're having a problem here. What about that?" And now I gather you can't speak to your advisory committee before meetings or give them any briefings or even call them for advice, for technical advice.

Saul: _____.

Aronson: Well, now you've got to separate it, the advisors. You can't be clubby with the members of your . . .

Saul: . . . the advisory board.

Aronson: Yes. What am I looking for. And money. The people who got in trouble last fall for keeping bad books.

Saul: Enron.

Aronson: The bookkeepers.

Saul: The accountants.

Aronson: The accountants, yeah. The accountants and the group can't get together. There are bad sides of that, but there's some awfully good sides to that, and we got the good sides to that. It was -- we had very, very good people, no question, and knowledgeable people.

Saul: Sure.

Aronson: But the Blood Bank, I mean, I'm sure in almost all those advisory committees, there'd be somebody from the Blood Bank there speaking or just listening. There'd be all sorts of people in there.

Then those meetings got huge, and I don't understand it. Yeah, I'm interested in it, but I don't know why the marketing people are interested, and you get 37 marketing people in there. It's become a less productive meeting. It's a very formal meeting. If you want to make any statement, you have to file with the secretary beforehand, and you can't just . . .

When somebody starts something and I don't think that's true or we have some more extensive information on that. You don't have that kind of meeting anymore.

Saul: Does it provide good information? I mean, does it still advise on issues?

Aronson: Yeah, yeah, but it wasn't, it doesn't advise as broadly. Yes, you have more "official" consumer representation, but you don't have the same free and easy discussions with the audience, who are seeing it from different sides, too, and it's not as much fun.

Saul: Great. One last question, unless you have something else that we can talk about in a little bit.

In your CV, it lists that you have received the PHS Meritorious Service Medal. I just wondered what that was for.

Aronson: I don't know. I think the citation had something about standardization of

factor 8. I think there were other things involved there. I don't know what that was for. Surviving. And I think I was involved with another award there, too, something, a group award of some sort, but I don't think I ever knew what it was.

Saul: Are there things I'm not asking about that I should be that we didn't talk about that are important to this story?

Aronson: I mean, the thing that fascinates me is the whole time frame. You can't use humans and you don't want to use humans, the development of the chimps, and then you moved on, and then you get a new disease and you haven't any idea about it, and the chimp model fails you in the inactivate patient. But if we'd done -- if the clinical experiment had been done a year earlier, it would have sunk the whole ship. That would have been it.

Saul: Very important timing.

Aronson: Yeah. But isn't that weird?

Saul: Yeah.

Aronson: I hadn't thought of that until I was talking to a lawyer. Geez, you know, if that had happened a year before, it would have been a disaster.

Saul: Mm-hmm. Because a lot of the _____ you don't know.

Aronson: Yeah. And that became, and rightfully so, the big issue. But by that time we'd solved the big issue before we knew what it was. And I thought, you tell that to the lawyers, and they don't like it, but I think we did a pretty good job on that, although our friends in France that go to jail; my friend,

Mike Rodale [sp.], is going to be accused of manslaughter or something in Canada. We like our scapegoats.

Saul: Yes, we do, and the legal issues are a whole 'nother story that I may ask to talk to you about later.

Aronson: But I think these are social issues, not legal issues.

Saul: Oh, yeah. Oh, absolutely, absolutely.

Well, thank you very much.

Aronson: I enjoyed every minute. I love to talk. I hate to listen.

As a historian of medicine, did you go to hear Donald Kennedy the other day?

Saul: I did not. I've been out of town for a couple days.

Aronson: It was a great talk. If you get a chance to hear him, it was very, very interesting. He's a very wise, knowledgeable, and thoughtful man, and what he did was draw a parallel in the biological investigation, biomedical investigation . . .

END OF INTERVIEW