

**History**  
of the  
**U.S. Food and Drug Administration**

**Interviewee:** John S. Finlayson, Ph.D.

**Interviewer:** John P. Swann, Ph.D.  
Robert A. Tucker

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INDEX

Tape	Page	Subject
1-A	1	Personal & educational background
	6	PHS Cancer Institute postdoctoral study – Sweden
	7	NIH biochemist assignment – protein turnover studies in tumor cells
	11	Defense & Civil Defense Departments' uses – human albumin
	14 & 16	DEAE cellulose protein chromatography
	17	Division of Biologics Standards (DBS)
	18	First criminal prosecution re biologic products under Public Health Service Act (Calise & Steinschreiber case)
	23	FDA & NIH enforcement strategy differences
	25	Immunoglobulins / immunoelectrophoresis
	28	National Blood Bank Act – legislative proposal
	33	Staff reactions - DBS transfer to FDA
	36	Branch Director, Plasma Derivatives – role changes
	37	Osaka University, Japan mini-sabbatical – horseshoe crab research
38	Teaching experiences - Introductory Biochemistry & Mathematical Preparation for the Biochemical Laboratory	
2-A	44	Transfer of NIH Division of Biologics Standards to FDA's Bureau of Biologics – Harry Meyer, Director FDA management changes
	46	Plasma protein fraction / albumin resuscitation fluid – military injury treatment use
	49	Hypertensive episodes caused by plasma protein fraction

	50	Cutter Laboratories bradykinin in plasma complications
2-B	51	Factor XII (B-XIIa) research and market removal
	52	Blood clotting Factor XIII
	53	Recall of plasma protein fraction
	59	Immunoglobulin stability research
	66	Rabies vaccine allergic reactions research
	69	Additional issues discussion combining functions of Biologics and Drugs
3-A	73	HIV/AIDS issues
	76	Chief, Hepatitis Laboratory assignment – issues & program accomplishments
3-B	80	Desert Storm HIV / hepatitis A immunization of troops issue with Saudi Arabia
	83	Hepatitis C carrier issues & research
	87	Blood Products Advisory Committee counsel
	89	Baxter Laboratories world-wide withdrawal of immune globin intravenous product
	92	Personal commentary on agency status, functions & leadership
	95	PDUFA (Prescription Drug User Fee Act)
		MDUFA (Medical Device User Fee Act)
		FDAMA (Food & Drug Administration Modernization Act)
	97	Orphan Drug Act
	98	Staff understanding of regulations
	99	Illustration biologics inspection – immune globulin manufacturer – quality assurance factors
	101	Post-FDA retirement activities

Interview with John S. Finlayson

June 11, 2009

TAPE 1, SIDE A

RT: This is another in the series of FDA oral history interviews. Today, June 11, 2009, the interview is being held with Dr. John S. Finlayson, and the interview is taking place in the Parklawn Building in Rockville, Maryland. The interviewers are Dr. John Swann and Robert Tucker of the FDA History Office.

Dr. Finlayson, as we begin our interview, if you could give us a brief overview of your early history, perhaps where you were born, attended your early education, and then, of course, your collegiate work later, and we'll go into your career from there.

JSF: Very well.

I was born in Philadelphia, Pennsylvania, although I never lived there. At the time that I was born, we lived in New Jersey, and before I was a year old, we moved to Delaware. It was there that I began school. But soon after that, we moved to Virginia, and then, later, back to Delaware, and from Delaware to New Jersey. And I attended public schools then in Delaware and Virginia and New Jersey. And then we moved again to Ohio, where I completed my high school training and entered into the local college, which was Marietta College, from which I graduated four years later.

JS: John, what did your parents do?

JSF: My father was a chemical engineer, and he specialized in pilot-plant work. Now it's the term that -- you're in FDA, you know very well what it is, but people in the outside world don't appreciate that that is the manufacturing stage between a laboratory discovery and making hundreds of thousands of pounds or gallons a month. There has to be a series of scale-ups, and that's what he specialized in. And he always said that if he did his job right -- he could have a thing up and running and not only producing but also making money in four years -- he would essentially be out of a job. Now, he might be assigned another job within the same company, but it would almost undoubtedly be at another location. So his prediction was that if he did his job right, he'd be out of a job in four years. And when you sort of take an algebraic average of my early life, that's just about the way it was.

So after sort of roaming up and down the Eastern seacoast until roughly halfway through my high school career, we moved to Ohio and I stayed there until I was out of undergraduate college. And then I continued the Midwest approach and went to the University of Wisconsin, where I got a master's and Ph.D. in the same department, the Department of Biochemistry. And this particular Department of Biochemistry was in the College of Agriculture. I say this because there were many different places where one could major in biochemistry at Wisconsin. It's now called the College of Agriculture and Life Sciences because I guess that brings in more money. But that's my education up to Ph.D.

JS: Wisconsin has a long tradition in biochemistry, of course, with people like

Steenbock and many others. Is that part of what attracted you to that school, or were there other reasons?

JSF: The main reason that I was attracted to the school was the fact that I entered undergraduate school as a pre-med major, and so I was assigned to a faculty advisor who happened to be the head of the biology department. And I had never taken a course in biology at that time, but I was still swaggering and confident that I was going to be an M.D. and cure all the ills of the world. But it turned out that not only had I not taken biology in high school, I couldn't get biology into my schedule as a freshman.

Now, going back to high school, in Marietta High School, there was a very unusual man, a one-man department of chemistry and physics, who taught the regular two semesters of physics, but he also taught five semesters of chemistry in high school, and this is a high school in the 1940s. I mean, you know, this is pre-Sputnik, pre even the Russians thinking about Sputnik. This man taught five semesters of high school chemistry. Now, nobody ever took all five because you weren't in high school long enough to get them all into your schedule, but I took three of them. And so, the way things worked out, I didn't take biology until my second year in college, at which time I was taking my sixth semester of chemistry. And in those days, biology was pretty much morphology and taxonomy and, shall we say, in comparison with chemistry, biology suffered greatly by comparison.

Nonetheless, the next year came, and I had to take something, so I took some more biology while majoring in chemistry and deciding the M.D. business was going to have to go. I was going to be a chemist. But I also kept taking more and more biology.

And finally, as I was entering my senior year, I said to the head of the chemistry department, “You know, I’ve never taken a course in biochemistry, and obviously I’m not going to be taking one here because I’m coming up in the odd year,” because biochemistry in this little college was taught only every other year. “But I think I’m interested in biochemistry. Where should I go?”

He says, “Wisconsin,” no question.

Now, he had gone to Ripon College as an undergraduate in Wisconsin, and he had a master’s from the University of Wisconsin, which I think he’d gotten in something like 1909, and there was no question. And so I immediately began to apply for financial support. And the University of Wisconsin was the first to come through, and, ironically, they came through with the most money of any of the universities to which I applied. So it was really one man’s suggestion and money that did it.

RT: Just to put this in perspective of time, you got your B.A. degree in Marietta College. What year was that?

JSF: Nineteen fifty-three.

RT: All right. And you had graduated from high school in . . .

JSF: Nineteen forty-nine.

RT: Yes. And then you went over to Wisconsin. What year did you do your master's there?

JSF: Let me see. It would have been right at the beginning of January 1955.

RT: Thank you.

JSF: The Ph.D. was awarded to me in June of 1957.

RT: I just wanted to get the time in that part of the history. Go ahead.

JS: Well, once you finished, what ideas did you have for life after Wisconsin?

JSF: Well, one of the things that was very big in young men's lives at that time was the draft, and so I was fortunately relatively young -- I was 15 when I started into college -- so I was able to get quite a way through college before the Draft Board had an interest in me. But once I got to graduate school, it was a true cat-and-mouse game. I had a 2S classification one semester, which is student deferment, and then the next semester I was 1A, which is most draft-eligible. And then I would go down and plead with the folks at the counseling center, and somehow I would get back into 2S. And then after one semester, because they had failed to renew anything, I'd be back in 1A, and this went on

through the entirety of graduate school. Dien Bien Phu is going on, the Hungarian uprising was not yet taking place, but there was a very unsettled world.

Anyway, the lady who was in charge of the Draft Board where I was registered, which is now Virginia because my father had moved from Ohio back to this little town where we had lived in Virginia, and he had remarried, and so his residence became my residence. The lady who was the secretary at the Draft Board there was actually secretary of another Draft Board, and she said I was the oldest draft-eligible man in both catchment areas combined.

Well, a day or two after I got my Ph.D., I got a letter to inform me that I had been awarded a National Cancer Institute postdoctoral fellowship to study in Sweden, and the day after that I received my Report for Induction notice. So, to answer your question, what was my post-Wisconsin thought, I spent most of that summer getting myself undrafted.

What I had to do was to ask for a personal hearing before my Draft Board, because these were faceless gentlemen whom I'd never seen before; everything was dealt with on paper. But when I met them, they were really quite nice and quite cordial and quite understanding. I mean, I was thinking I had the temerity, after being deferred for some seven years, to ask for another year. But the main problem was getting a quorum because people were taking vacations over the summer. Anyway, they allowed as how I could have another year, and so on September 1<sup>st</sup>, 1957, I got married, and September 5<sup>th</sup>, 1957, we set sail for Sweden. And it was while I was in Sweden that I applied for a Commission in the U.S. Public Health Service.

Now, one of the things you had to put down on the application for a Commission in the Public Health Service was, if you are commissioned, if we smile on you, where would you like to be assigned? Well, I agonized over this because everybody knows, if you put your first choice as a first choice on a government form, that's the kiss of death. You're never going to get it. So I thought of three places that I would be really quite happy to work as a biochemist. One was NIH; one was what no longer exists, the Robert A. Taft Sanitary Engineering Center in Cincinnati; and one was the CDC, which stood for different things but still has the same initials, in Atlanta. And so, as I said, I agonized, now, how should I try and game the system? And finally I figured I don't know how to game it. I just have to put it down straight. Number one, NIH; number two, Robert A. Taft; number three, CDC. And, sure enough, I got assigned to NIH.

Now, I didn't know until I got here that the part of NIH I was assigned to was the lowest in the pecking order at NIH, but it didn't matter. For a biochemist, coming to NIH was like being invited to the gates of paradise. I mean, there just, in the '50s, wasn't any place in the world for biochemists that came close to NIH.

RT: When you were in Sweden, is it correct that you were a National Cancer Institute postdoctoral research fellow?

JSF: Yes.

RT: That was really the assignment of your choice at the time.

JSF: That's right.

Now, it turned out that I was even able to broaden my experience there because when I had made my proposal in the application for this postdoctoral fellowship, it was to work on protein turnover in tumor cells. And they had approved that.

And when I arrived, my mentor said, "Well, I've ordered the radiolabeled amino acids that you'll need. They come from England. It'll take about 10 days. Would you be interested in doing some experiments on nucleic acid biosynthesis in these same tumor cells during the time we're waiting for the radioisotope to arrive from England?"

I said, "Of course. That's what I'm here for. I'm here to learn."

And he said, "Fine."

So I started to work on the business of how did these little cells take in very simple starting materials and incorporate them into a whole variety of things on the way up to making nucleic acids. And about April of the following year, that's 1958, I was finishing up and submitting a manuscript for publication and was ready to get back to working on protein turnover, which I did.

JS: And that, by the way, was related directly to what you'd done in your dissertation work?

JSF: No, it wasn't. And people will think you planted this question because you may ask, why did you apply to work at an institute of radiophysics, of all things? I mean, after all, you're a biochemist. And the professor in -- in European departments, there's only

one professor per department -- the professor who was the reigning authority in the Institute of Radiophysics at the Karolinska Hospital was Rolf Sievert, after whom the unit, The Sievert, is named. So it was really a radiophysics institute. It just happened that the man I worked for, Arne Forssberg, was interested in radiobiology. I wasn't interested in radiobiology, but I was interested in his work because he had done some, I thought, fascinating studies on hunger regulation. And one of the minor things that I had worked on during my dissertation had to do with that, and I thought, if I could use radioisotopes as tracers, maybe we could get a handle on actually what's going on, how some animals learn to eat their entire daily intake in a short period of time, whereas others just don't seem to get the point or figure this out.

Well, I wrote to him about this, and he wrote back and he said, "I think this is a wonderful project. The only thing is, it'll take more animals than we can house in our lab. But would you like to work on protein turnover?" So that's how I got the topic of my research proposal.

Now, somewhere between when I started to work in Dr. Forssberg's laboratory and when we'd finally gotten around to working on protein turnover, this very tall and very slender, very young man came in and yelled out in rather profane Swedish, "Does anybody in this blankety-blankety-blank institute know how to measure cholesterol?"

Well, I'd learned enough Swedish to know what he said. I said, "Young sir, I cannot tell a lie. I just did a thesis, a large portion of which was on, in fact, measuring cholesterol."

So it turns out this guy was at the Royal Veterinary College, which in those days was in Stockholm, just sort of a stone's throw away, on the other side of a little body of water, so I actually got to work there too.

So I think the government got its money out of me because I ended up publishing three papers: one on the pathway to synthesis of nucleic acids in tumor cells; one on protein turnover in tumor cells; and one on cholesterol levels in obese dogs and dogs with various diseases.

JS: Well, it was important, I think, to find out what it is you were working on during your postdoc, or the first part of your postdoc there, before ending up with your Commission at NIH.

But getting back to that move, now, you're back at NIH.

JSF: Well, I mean, I had never been at NIH before.

JS: Right. Well, you're at the flagship.

JSF: I'm back in the U.S., and after a month of sponging off my parents, I got a telegram saying, "Report on October 20<sup>th</sup>, 1958, to NIH."

JS: And you mentioned the component at NIH where you were situated was not the highest in the pecking order. Which part of which institute were you in?

JSF: Well, see, it wasn't even called an institute. I mean, it was, for all practical purposes, an institute. It had all the components of an institute, but it was not called an institute, and that meant a great deal to the powers that were. It was the Division of Biologics Standards. And, you see, it wasn't really an institute; it was a division.

To me, it didn't matter. I was at NIH. I was in paradise, and you could put whatever stamp over the door you wanted.

Now, I don't know. Would you like me to start into what I did there, or . . .

JS: Well, I think it would be interesting to see what it is you were doing there, what kind of tie-in it had with what you had been doing up until that point.

JSF: All right.

Well, suffice it to say that on the thing that actually took the major part of my time as the Institute of Radiophysics, I was not, for the most part, handling nucleic acids. I was working on things on the way to nucleic acids. In other words, if you gave a very simple biochemical as a precursor, what did it have to form in order to get itself organized in order to make nucleic acids. So I was doing a lot of ion-exchange chromatography to separate out these things.

Now, I had, of course, used some chromatography in my graduate research work, and I had done more in coursework, so that formed part of the background that I'm going to get to in just a second.

When I arrived in the Division of Biologics Standards, I was assigned to the Laboratory of Blood and Blood Products, and I think that's an important thing because I was assigned to blood and I stayed there even to this day. It's changed its nomenclature, but that's where I remain.

Within the Laboratory of Blood and Blood Products, I was assigned to the Coagulation Section. See, we have to use NIH nomenclature; that working unit was called a section. And I won't say that the Coagulation Section was small, but when I arrived, its population increased by 100 percent. In fact, we were so small that there was no section chief. We had to borrow a section chief from the section across the hall, which was the Blood Derivatives Section, as it was called in those days. And the section head there was an M.D., but he was extremely well trained in biophysics, and he said to me, "Would you know how to do moving-boundary electrophoresis?"

"Yes. I did that for my graduate work."

"Well, do you know how to do analytical ultracentrifugation?"

"Yes, I did that as part of my graduate work."

"Ah. Do you know how to do chromatography?"

"I had a year's worth of chromatography in my postdoc."

"Yes," he said, "but have you done protein chromatography?"

I said, "Well, I did a little bit of it in my graduate work by the method of Tiselius, who was the inventor of moving-boundary electrophoresis. He had moved on to other techniques in protein chemistry and came to Madison and gave a talk about chromatography on hydroxylapatite, and he was kind enough to give me one of his

manuscripts before publication. And so I synthesized some and carried out some chromatography on it, although I couldn't claim I'd made any big breakthroughs."

"Well," said this borrowed section chief, "have you ever done DEAE chromatography?" See, in Washington everything breaks down into three-letter or four-letter acronyms. It stands for diethylaminoethyl cellulose, a derivatized cellulose which allows it to work as an anion exchanger.

"Have you ever done DEAE cellulose chromatography?"

I said, "No. I've heard about it, but I've never done it."

He said, "Well, that's what we want to do."

And I said, "Fine. I'm your man. I'm here ready and willing to help. What's the first thing you'd like to have me do?"

He says, "Synthesize the DEAE cellulose," because you couldn't buy it commercially.

The first full-length paper on the ion-exchange celluloses, both anion and cation exchange celluloses, had been published in 1956 by its inventors, Elbert Peterson and Herbert Sober, at the NIH. So, you see, I really was in Mecca. So I set to work and I synthesized it, and I packed a column with it, and the column had a flow rate of exactly zero.

Well, I won't bore you with the intermediate details, but finally I had an opportunity to meet Drs. Sober and Peterson, and Sober immediately handed me off to Peterson, who was the chemist, Sober being the biochemist, and Peterson sort of grilled me: Well, did you remember to do this and this and this and this and this? And I kept saying, "Yes, yes, did that, did that, did that."

Well, finally he came and said, “Well, did you sift the cellulose before you started?”

And I said, “What?”

And he said, “Oh, did we forget to put that in the paper?”

Well, eventually I went back and reread the paper, and if you could read between the lines, you could figure out retrospectively, yes, it should have been sifted, but no place did it say thou shalt sift. So, I dumped what I had made. I started over again and synthesized the DEAE cellulose, and it worked very nicely. And then I had to teach myself, from their papers, how to use it.

So after, I would say, a year, I was pretty good at performing protein chromatography on DEAE cellulose, this quite new field. I mean, I was surveying the literature of the world assiduously, and the world’s literature by this time was up to about eight or nine papers.

So, at this point, the head of the Laboratory of Blood and Blood Products came to me, and I think he was actually in panic that after another year, I would have done my two years’ obligatory service time as a commissioned officer in the Public Health Service, and he was afraid I was going to leave without having published anything to the glory of his laboratory. And so he said, “Well, now you should do some bread-and-butter work to use this wonderful technique,” and I’m thinking flattery is a very good approach, sir.

So I said, “What did you have in mind?”

He said, “Well, you could do this, you could do this, or this.”

And I picked one of those, and the thing that I picked was very closely related to the political situation at that time, which was the Cold War. The Defense Department and the Civil Defense Department were quite sure that we were going to enter a nuclear cataclysm with the Soviet Union and that people would be literally fried in the streets and they would have to undergo trauma resuscitation, and the thing that they would be resuscitated by was various solutions of human albumin. Now, I never figured out, if there was going to be this massive destruction, who was going to be around to administer the stuff. But I was a biochemist; I wasn't asking these great public health questions.

Well, this gentleman had foreseen that this was going to come up, and he had foreseen something else even more important. The Department of Defense, primarily the Army, ordered and stockpiled very, very large quantities of human albumin, and it was given a dating period. And the Division of Biologics Standards, which was the regulatory agency responsible for biologics, said, "Well, if you not only store it refrigerated, but store it in a hermetically sealed metal can, you can have an extended dating period." Well, that, of course, they did. And guess what? The Russians never attacked, so the stuff outdated.

Well, the Army didn't want to throw away such expensive stuff, so they said, "Well, let's recondition it." Now, reconditioning it simply meant popping the top, giving it another sterile filtration, taking it through one physical step, and rebottling it.

How were they able to get away with this? Because the tests that were being applied didn't see any difference between it and the original test results when it was freshly made.

Now, this farsighted lab chief realized that someday methods were going to become available that would show something, and so he had arranged to have, under contract, made and stored a great variety of albumins, albumins made from fresh human plasma, albumin made from dried human plasma, or made from dried UV-irradiated human plasma, and then prepared as a freeze-dried powder . . .

TAPE 1, SIDE B

RT: We were just speaking of prepared as a dry solution.

JSF: No, as a dried powder.

RT: Powder.

JSF: In 5 percent solution or 25 percent solution, and then stored at 5 degrees Celsius; in other words, refrigerator temperature, room temperature, or elevated temperature, at 32 degrees Celsius, approximating what it might undergo in a ship's hold, for example.

As you can see, this is a lot of experimental groups, and the remarkable thing was, chromatography on DEAE cellulose was quite powerful in revealing changes that the standard methods, the ones that would show up in the *Code of Federal Regulations*, couldn't detect. Furthermore, I found that if you used DEAE cellulose chromatography in consort with analytical ultracentrifugation, it was even more powerful. And so the first

paper that I published as an employee of the Division of Biologics Standards was on albumin, despite the fact that I was in the Blood Coagulation Section.

Now, maybe you should direct where I should go from here.

JS: Well, it certainly was important to find out about what your initial research as a commissioned officer working for DBS was.

JSF: Right.

JS: Now, there's a context here, too, that I think we might also hear about, if you care to share any of this, and that context is, you know, DBS's place in the structure at NIH. Clearly this was not long after the Cutter vaccine disaster in 1955 in which live virus was introduced during the initial release of the Salk polio vaccine. There were a lot of changes that came about because of that therapeutic disaster, one of which had to do with regulations over the ways these sorts of products would be produced. But also there were administrative changes dealing with the regulation of biological products. This had nothing necessarily to do with blood, but it did have everything to do with biologics regulation and the place of that function at the NIH campus. And I wondered, as a new employee, just within a couple, two or three years after this happened, if you had any sense of what had been going on in terms of the culture of the institution you were working in.

JSF: At the time I arrived, I don't think I had much. I mean, of course, I was aware of

the Cutter incident and I was aware that the Laboratory of Biologics Control had been extracted from what was in those days called the National Microbiological Institute of the NIH, and it had been raised to division status to make the Division of Biologics Standards. Interestingly enough, that very same year, which was 1955, the National Microbiological Institute got a new name, which was the National Institute of Allergy and Infectious Diseases, NIAID, which name it carries to this day.

I think that my appreciation for these kinds of changes only came about years later. But one of the events that happened after I'd been around for about four years was what I understand was the first criminal prosecution under the Public Health Service Act. In 1944, the Public Health Service Act was written, and that was essentially a massive update of the Biologics Control Act of 1902, which was when the regulation of biologics began.

JS: So this would have been the first case brought in about 60 years of regulation over biological products.

JSF: My understanding, yes. Now, obviously, there had been enforcement actions that happened before then, because I think . . .

JS: Licenses had been suspended, no doubt about that.

JSF: But I think, as I understand it, this was the first criminal prosecution, and a couple of gentlemen in the New York-New Jersey area were doing a variety of things, and I

think they were doing so many things that were counter to the Public Health Service Act that it would be easier to name what they didn't do. But, I mean, among the things that they were doing is they were shipping across state lines without holding a license. They were shipping both dried plasma and blood products. They were often re-dating blood, blood which had expired. They would just put a new date on it and reissue again.

JS: That's an easy solution, isn't it?

JSF: That's right. And it turned out, I think, that a hospital nurse actually recognized a unit of blood as one that she had seen before, and that was one of the initiating moments.

But it turned out that the hospitals just loved these gentlemen because if you needed Rh-negative blood at three o'clock in the morning, they could have it right there in their refrigerated truck. The problem is, the label said Rh-negative blood, but no telling what it was. So not only were they changing the dates, but they were actually changing groups and types.

So I was only at the very, very periphery of this happening, but one of the things that the lawyer for these defendants tried to say is that there was no authority to prosecute them because blood did not fall under the Public Health Service Act. And the argument of the government lawyers was, the Act says very clearly, a therapeutic serum or analogous to a therapeutic serum, and they felt that there's no question that blood was analogous to a therapeutic serum.

Well, in that particular case, my understanding . . . You know, I keep saying "my understanding" because I have never sat down and read the transcripts of the judge's

ruling. My understanding is that the judge ruled that blood was analogous to a therapeutic serum and that the Public Health Service Act was applicable in these cases.

But my understanding was, not so long after that, in a different state -- this took place in the New York District office -- but later a judge ruled the opposite way, so there was some modification of the Public Health Service Act at some point to make that explicit.

RT: Do you remember what, in case someone would be interested, what case that was or what citation in court?

JS: I think the case that you're talking about, John, is the Calise case.

JSF: Calise and Steinschreiber.

JS: There was a case later, in the '60s.

JSF: It was in Florida, wasn't it?

JS: Yes.

JSF: Where the judge ruled the other way.

JS: There's a lot going on here. This period of the '60s is a fascinating one from

many standpoints, but certainly from the standpoint of blood and blood banking, and it's also on the verge of the function being transferred, all biologics functions being transferred to FDA. And that's another story, because then FDA law becomes, well . . .

JSF: I should say, my understanding is, again, in this very first case, it was ruled that the drug law could apply to biologic products even though biologic products were regulated under the Public Health Act and pharmaceuticals were regulated under the Food, Drug and Cosmetic Act, that the biologic people, when appropriate, could apply the FD&C Act.

Now, that really didn't affect me in any substantial way, but I think that that was the first ruling to that effect.

JS: Now, I want to follow this up with one question, and this may or may not be relevant, because I know what you're doing in DBS at the time, you know, you're pretty focused in doing important work that you've already talked about. But it does make one wonder, in a regulatory agency -- and that's one of the things that DBS and its predecessors do, they regulate biological products -- there was a provision in the original law, of course, in 1902, that you could bring cases to be prosecuted. This is not something where hands were tied. But we have 60 years under this law until the first case. And Joel Solomon I think also has mentioned the same thing, that no case had been brought until this, the one you described.

But I'm curious if you have any ideas or if you've wondered why it is. I mean, was the industry that clean? Or why it is that so much time had gone by before you actually saw a court case come out of this legislation.

JSF: I have no idea. And in the period there of 1958 to 1962, the vast majority of my regulatory work had to do with products that were actually intended to dissolve clots when they formed where you didn't want them, sort of the other side of the coin from blood coagulation. So I had a rather worm's-eye view of life and what went on.

Now, one of the things -- I'm jumping ahead -- when it became FDA, that the FDA hard-liners criticized the newly arrived biologics people for was that they were collegial; their relationship with industry was collegial. And the implication was that this was really a bad thing, because you should go in with your badge shining and your guns blazing, and that was the only way to get compliance; whereas the philosophy, I think, at the time, and certainly as I began to be involved in inspections myself too, that you could get compliance if the regulated industry respected you as a scientist and as a knowledgeable person. I mean, I could cite so many examples about that that we'd be way ahead in our timeline here.

What recently fascinated me was when I went back and I read *HIV and the Blood Supply*, which was published in 1995, one of the criticisms that the IOM leveled at the FDA, at least in what we call CBER today, was that the relationships were collegial even though by that time biologics had been part of the FDA for 23 years. So I don't really know that there is a moral of the story, but I just found that this was a little bit amusing.

Anyway, I may be off the track now, so . . .

JS: No, no. But I think this is, these are questions that one thinks about, about the culture of enforcement or how one approaches it, and the biologics function came from a very different part of the government than FDA did, NIH.

RT: I think there may be kind of a basic difference in that FDA people, at least in earlier times, were instructed you're really not there to correct, to counsel the company. You're there to tell them what's wrong. It's their responsibility to make the correction. Whereas I think on the other side was a more education approach, to help educate rather than adjudicate in court.

JSF: I think that's true. I mean, I think the feeling was, if we're going to license product, it should be a good product. Now, obviously, you can't violate any confidential information and say, "Oh, Mr. Company B, Company A makes it this way. Why don't you do it that way because he's got a good thing going." But, at the same time, if you had something from your own research that clearly demonstrated they were just making a fundamental scientific mistake, we always felt that it would be unconscionable not to point this out. Now, there sometimes was the business that you led a mule to water and you couldn't make the mule drink no matter what you did. But I think in a very substantial number of cases, you would just see the light bulb go on and they'd say, "Oh, why didn't we think of that?" And they might go home, do their homework, and then do the basic engineering, and you felt that you had actually done something useful for the ultimate recipient of the product. So I think you raised a very good point there.

JS: Well, when you arrived there, you were not working in an academic laboratory. I mean, DBS, its essential function was that of a regulatory agency, unlike every other component of NIH.

JSF: Right.

JS: Did that register in a way that you can remember? Did you give that a second thought?

JSF: Well, yes, I did. And it was as if we had two jobs. We were supposed to be doing research, albeit directed. I mean, if we decided that we were going to study the metabolism of cholesterol by some exotic microorganism, that might not have gone over too well. But within what we were supposed to do, we were supposed to do research, and a substantial quantity of research, of the same quality that NIH was turning out, and do this regulatory job. So we felt that we had two jobs, and we had to do both jobs in order to be doing our jobs.

And my colleague and I, three weeks after I raised the population of the Coagulation Section by a hundred percent, we got one more fellow, and I never let him forget that he arrived after I did, but he never let me forget that he'd been in the Public Health Service for a year before he arrived there, so he had seniority.

But he and I often used the expression, "We see more of the elephant than the other people at NIH," you know, the blind men and the elephant. And he continued,

“The NIH people are going forth and doing their research, but they just somehow assumed that the proteins that they wanted to buy from a biochemical supply house magically appeared in that bottle, that the protein solutions that the NIH pharmacy would be dispensing just magically appeared in those bottles.” By contrast, we had an appreciation of the fact that they had to be made, they had to be made to specifications, they had to be made by something when there are narrow tolerances, and they had to be quality controlled, and this didn’t enter the NIH thinking.

So let me give you an example, and I wish I could come up with the year, but it would have been toward the end of the ‘60s.

Dr. John Fahey, whom I met quite early in my career, who was in the National Cancer Institute, decided with, I believe, the company, the one that turned into Melpar, but I don’t know what its name was at that time, over in Virginia, to set up a laboratory to which physicians could send patient samples, and they would do immunoelectrophoresis and tell you the distribution of the patients’ immunoglobulins into the various classes that were known at that time. And the classes that were known at the time were what today we would call IgG, IgA, and IgM. Of course, Dr. Fahey himself complicated the situation by discovering IgD, and then somebody else came along and discovered IgE, which seems to be floating around in our veins simply to cause allergy.

In any case, he asked me to become involved in being one of the sort of scientific visitors to critique the operation of this laboratory which was set up with National Cancer Institute funds in this company over in Virginia. And in addition to times I went over there and the times I spent reading some of their drafts, there were also some rather large meetings that took place on the NIH campus. Although this operation was set up for

physicians to be able to have their patients' material assessed by techniques that certainly an ordinary clinical pathology lab wouldn't set up in those days, there were people at NIH interested in fundamental immunology that also wanted to know what was going on there and would like to have been able to send a sample every now and then to have it checked out. You know, how pure is this IgA, or whatever it is I'm making in my lab?

And so I can recall one meeting that took place in I would say the Masur Auditorium, we call it today, in the NIH Clinical Center, with, I'd say, the auditorium at least two-thirds full of interested folk. And they did get the concept, which, of course, was our daily bread, that there should be reference standard preparations, because, obviously, that was one of the ways that we could calibrate tests that the manufacturer should do and that we should do to make sure each lot met specifications. So the audience seemed to get that.

And then one of my colleagues, who was a little older, a little wiser, said, "Well, now, these reference standards, how will you maintain them? Are they going to be frozen solutions? If so, what should be the protein concentration in there? Or should they be freeze-dried, and, if so, how much should there be per ampule, and should they be in flame-sealed ampules or should they be in stoppered, capped vials?" Jaws sort of dropped. What is this guy talking about? This is a foreign language.

Then he went on and he said, "And by the way, you were talking about" -- I don't remember which of the immunoglobulins it was, but say IgA . . . "I understand this is a very difficult material to purify to homogeneity. How much do you have?"

“Oh,” somebody said, “I’ve got this much in my lab. I can donate it.” Another one said, “I’ve got this much in my lab.” Well, anyway, you added them all up. They had about 60 micrograms total.

So this is what I mean by we saw more of the elephant than the NIH people. And, again, it was a very, very mixed bag because we met people, some of whom, of course, we knew from our academic work, and became very close collaborators with them, and so it was a wonderful relationship, very productive for everybody, and I’ll elaborate on this later if you wish.

But there were other folks who would sort of come to us cold, I mean NIH folks, saying, “Well, my supervisor said that you folks might know something about this.”

And we’d say, “Sure, we published this and we published this, we published this, and we have this material and this material we can share with you.”

And they’d say, “Gosh, I didn’t know you folks did research.”

Well, you know, years would go by, and decades, and they’d still be saying the same thing. You know, try as we might, our light always seemed to be under a bushel.

JS: The nature of where you’re situated, though, you think? Right? That has a lot to do with it maybe?

JSF: Yes. Well, I mean, NIH is a resource that FDA couldn’t buy. I mean, if and when biologics goes to White Oak, there could be the delusion that people will sit at their computers and interact with everybody, but when it’s gone, it’s gone, and those relationships will never be the same.

JS: Within the NIH community, between the institutes and the FDA, the CBER people there.

Well, we do want to talk more about that because I think that's an important point to make as we try to centralize the agency into one place, or semi-centralize it, since the Foods people have their own campus, building, rather.

But we're moving through the '60s, and, of course, there's a lot going on in the world of blood outside, with blood banking. We're on the verge here of seeing things as the '60s end and in the early '70s, the situation of the blood supply causes enough consternation among people, including people on the Hill, that Representative Victor Veysey introduces the National Blood Bank Act, which would ostensibly correct many of the issues with the blood supply.

RT: Did that legislation come out of the Congress?

JS: It was a bill; it was never passed.

Also, in fact, this started early, with the '50s, the Joint Blood Council with the American Association of Blood Banks, the Red Cross, AMA, and others trying to promote their own similar interests, but that's a rather short-lived attempt.

I don't want to get ahead of where you're working; you're still in the blood group. But as the '60s come to an end and it's in the early '70s, you're still working in the same position you were as a research chemist in the Laboratory of Blood and Blood Products.

JSF: Right.

JS: Until 1972.

JSF: Right. And as you diagnosed it, the mere fact that I was in the Coagulation Section does not mean, by any means, that I worked only on clotting factors. But practically everything I worked on was a protein, so the technology was readily transferable across the lines there.

JS: But these were, as you said, I think maybe before we started the tape, happy days for you.

JSF: Yes.

JS: You were very happy working at NIH.

JSF: I was very happy. I mean, I was putting in 16-hour days, I would say, on average, and was delighted. I mean, I couldn't wait to get to work in the morning. I hated to go home at night. More nights than not, I'd come back after I'd get the kids to bed, and it was just a wonderful time.

JS: Your supervisors were very supportive of your work, I take it?

JSF: Well, they kept paying me. I mean, I guess the supervisors tended to come and go. There was a certain amount of turnover that took place, and the supervisors were, to say the least, heterogeneous.

The first lab chief of the Laboratory of Blood and Blood Products was a very active man, and when the Calise case came along, he just thoroughly enjoyed playing cops-and-robbers there. But he sort of left the scientists in the Coagulation Section alone, and on maybe one day a year he'd come down with some outrageous idea, trying to stir up the troops. But the other 364 days a year, you could work.

JS: You were left alone. That's a good thing, right?

JSF: Yeah, we were left alone.

And then when he retired, he immediately came back at a level closer to the director of the DBS. The man who had been his deputy moved up. This was a man who had been in on the ground floor of the research that had actually created the plasma derivatives industry. At this time I'm not in the Plasma Derivatives Section yet or Plasma Derivatives Branch or whatever we called it. But, of course, I'd been working on the most abundant plasma derivative, albumin, all that time. This man had been on the ground floor, but he had simply lost interest in the science of it. So he really didn't offer any support at all, but we sort of, I guess, harnessed his lackadaisical approach to life, sort of migrating around him and doing what had to be done.

And so, as I say, there was some, I mean, there was a lot of turnover in the position of the head of Blood, and some of the people were very, very good and some were not very good, and some were horrid.

But as we got into the early '70s, of course, there arose in the scientific community a great deal of interest in the Division of Biologics Standards. For some 12 years, when I'd go to a meeting where biochemists would congregate -- often these took place in Atlantic City, if you can imagine there was an Atlantic City before there was gambling -- they'd say, "Oh, where are you working now? What did you do after you left Wisconsin? Where are you working?"

I'd say, "At NIH."

"Oh, oh, you're at NIH," and then they would sort of genuflect.

And then they'd say, "What institute are you in?"

I'd say, "Division of Biologics Standards."

"Oh, very interesting, I'm sure," as they would wander off to look at the exhibits.

Well, literally, in about 1971, these people would start congregating in clouds around me, saying, "Hey, we read all these articles in *Science*. Nicholas Wade writes an article every week. What's really going on?"

"All I know is what I read in *Science* myself."

JS: Well, there was, obviously, there was a lot going on in the Division at the time.

JSF: Oh, indeed. And, you see, one of my neurological defects, or whatever you want to call it that I had, I have never been able to develop a shred of interest in politics.

You mentioned Joel Solomon, the late Joel Solomon, and some of his writings. Joel, I think, had three lives in Biologics. He was there when I arrived, and then he left, and then he came back, and then he left and he came back again, then he left again. Joel just *loved* the politics of blood, the National Blood Program and all that went therewith. He just reveled in it. I mean, he was a very, very knowledgeable bench scientist when he arrived, and he did not have a doctorate. But after he reappeared with a doctorate degree in hand, he sort of treated that as the union card and he would never have to do another experiment for the rest of his life, as opposed to me, who was dragged kicking and screaming out of the lab and into management.

So to this day, I fall asleep in these political debates. But it was even more so in those days, where all this action was going on that was being written up about the turmoil in the Division of Biologics Standards, and my feeling was that, fine, but what pH is needed to elute the protein?

JS: Well, this is also the time of all the turmoil in the Division, but this is also a prelude, and in 1972 the function is transferred to FDA. I guess what we'd be interested in hearing about is how, personally, notwithstanding what you just said about the interest in political issues, but I guess, personally, what did you think about that? And also, for example, did you think this would change the way you do your work or change the thrust of what your function was at DBS? So your personal sense of that, and also if you and your colleagues there had discussions about this and what this would mean for the Division.

JSF: Well, I would say that the greatest thing that happens -- and we see it happening in the world today, the automotive manufacturing and so forth -- is that the unknown always brings about uneasiness, and especially if the unknown is going to be initiated or participated in by a culture that's quite different from your own. And so I don't know that we actually had any great, long discussions about how this is going to affect the way we do our work. I think our idea was, we have to keep doing what we know has to be done and see what will happen.

I think that certainly most of the people that I interacted with, which was by no means all 250 or however many people were in DBS, most of the people I interacted with felt that leaving NIH administratively and going to FDA was not a good thing, because we felt that we were not drug regulators, except incidentally. And we were not knowledgeable about pharmaceuticals, except incidentally, in those fundamental functions like sterility testing and packaging testing and safety testing and so forth, which certainly cut across all of them. But there was just this sort of feeling that this is a different culture, and of course they felt the same way about us. The people who actually had to go in and make drug buys thought that we were just a bunch of long-hair academicians, sort of super-consultants to the industry or something like that. And I would say that probably a couple of years went by before anything really changed at the worker-bees' level.

And one of the first things that changed is somehow at NIH, there was this culture shift in the early '70s, where fundamental research no longer had such a good name, but applied research became a great thing, and I'm sure this had to do with some kind of

congressional activity. But suddenly at NIH, applied research was getting more money than fundamental research. Well, I mean, let's sort of wag our tails and say, "Hey, this is what we've been doing all the time. We do fundamental research when it's necessary in order to accomplish the applied objectives, but we walk back and forth across that line and think it's a good thing to walk back and forth across that line from applied to fundamental."

But I would say it was several years before the worker-bees even began to see what I'll call the line-inspector FDA people. I mean, we kept doing our own inspections. I wasn't inspecting at the time except on a few *ad hoc* situations that I got called into. But the people who did a lot of inspections continued to go out on their own inspections. And gradually, I would say, it was almost in the late '70s before we began to see enough of each other to realize that, hey, they really do know something that can contribute to the way we do business, and if we can just get them to calm down and teach them some of our nomenclature, they can profit from what we have to tell them.

So I think that there was a considerable period, at least from my viewpoint, where not a lot happened, and then there was this sort of circling of the heavyweights in the middle of the ring, trying to see what the other is going to do -- is he going to feint or actually throw a punch -- and then a gradual development of mutual respect. So I think it was not even a stepwise process, more like a gradient.

JS: Okay.

You were a research chemist in the Laboratory of Blood and Blood Products. You're now in the Division. So, is it simply a name change?

JSF: At that point, in 1972, it was just a name change. In other words, what had been called a Laboratory was now called a Division; what had been called a Section was now called a Branch. I should put a little asterisk by that and say that about 12 years later, somebody pointed out that branch is actually defined somewhere in some manual of operations that unless you have a certain number of bodies, you can't call yourself a branch. And so the man who was the acting head of the then Division of Blood and Blood Products at that time said, "Okay, but I've also done my homework and found that there's no definition of a laboratory, so all you people that were branch directors, bingo, you're now lab chiefs." So it was solved by nomenclature. So from '72 to '75, I was essentially doing the very same thing, but just different names attached to it.

RT: When you were designated as a chief, were you more administrative in your duties than operationally research oriented?

JSF: The big event in my life I guess came in 1975, when I moved from Coagulation, now called Coagulation Branch, to what was called in those days the Plasma Derivatives Branch. In other words, I moved about 50 feet down the hall, and instead of being able to come in in the morning and do my happy thing and maybe have one technician at my disposal, I was responsible for a dozen people, two of whom would always be fighting with each other over three square feet of cold-room space or some equally disgusting thing.

JS: Before -- let me just stop this for a moment.

[recorder turned off and on]

RT: I believe that's one of the dilemmas that probably is experienced not only by research people or laboratory science people, but also by inspectional people that are folks that don't like to get into all this administrative stuff and really enjoy the basic work better. We've even had some people go back to the field as inspectors.

JSF: Well, now, I mean, I was able to do a bit of research at first, when I became the Branch Director of Plasma Derivatives, but it very quickly eroded because, as I have said to several people who asked me about my historical career, that in the first six months as the Branch Director of Plasma Derivatives, I read more package inserts than I had the entire 14 years, or 17 years, I guess, previous to that. And, of course, every one I read, I found things that were wrong with it and felt they should be corrected as soon as possible. So my hands-on research sort of decreased exponentially.

Now, over the period, I'd say '76 to '86, I certainly interacted with some magnificently talented researchers who were doing more than their fair share of regulation at the same time. But they were hands-on in the research. I was just sort of giving an idea here and there and a comment here or there or helping with a calculation or helping write a paper or whatever. They were having fun and I wasn't.

RT: I think during that period, you also were pretty active in doing some lecturing and

I think an appointment for doing something over at Osaka University in Japan. Was that in relation to the work that you'd been doing prior to that time?

JSF: Yes. Well, let's make these two separate endeavors because one went on for a long, long time. Let's talk about the work in Osaka. That was only about three and a half months, and so I say I'm really not sure why, when I asked if I could take this mini-sabbatical at the invitation of the government of Japan, they agreed for me to do so. Maybe it was figured, well, it was summer and maybe things would be quieting down and the industrial people would be taking vacations, and so I could go off and play.

I was invited to work at the Protein Research Institute of Osaka University, which, about the time I got there, had moved way out from the town of Osaka and was out in the country, along with a few other university departments. And one of the things that they were interested in, which the Division of Biologics Standards and then, later, the Bureau of Biologics in FDA was interested in was the horseshoe crab. The so-called *Limulus ameobocyte* lysate test for pyrogenic substances had been discovered and was useful and of interest. And there was, of course, the question of when could and when could it not be used as a substitute for the rabbit pyrogen test. But people were just barely asking fundamental questions, like what's the basic biochemistry of this, you know, why does it work, and what would keep it from working. And the horseshoe crab that people collect up and down the Atlantic seacoast is *Limulus polyphemus*, whereas the one that's in Japan is closely related but a different genus and species. It's the *Tachypleus tridentatus*, and that was one of the things that the laboratory where I went was very much interested in. So among the things that I worked on during the time there

was the clotting system of the Japanese horseshoe crab, and we made a little progress, although in three months it's just one little cog in a big wheel. And I also worked on some other clotting proteins as well. I certainly learned some techniques that were very useful, but I wasn't the one that got to apply them, you know, when I got back.

Now, I think that's about all I can say about the work I did in Japan because, as I say, it was a very short period of time and very restricted. It certainly helped me charge my battery up as I came back.

Now, the teaching began quite early, in the very late summer of 1961. One of the technicians came into my lab, and she was just absolutely furious, I mean, literally, smoke was coming out of her ears. And she said, "This is the third year that I have gone up to the" -- it has a wonderful name -- "the Foundation for Advanced Education in the Sciences, Inc." I always thought they ought to get a football team because I want to know what the cheers would sound like. But she said, "This is the third year I've gone up there to register for Introductory Biochemistry and the third year I've been told it's not going to be offered because there's no instructor."

I just said, "Calm down, calm down, calm down."

Anyway, she stormed off, and a few minutes later she's back in, equally furious. "Why don't you teach it?"

And I said, "Are you out of your mind?" I mean, I haven't taken introductory biochemistry for something like eight years, and I haven't ever taught a course that comprehensive. Anyway, maybe the sun was too hot and fried my brains, because by the following Monday I'd decided, "Well, maybe I ought to do this."

So I called up Chris Anfinsen, who, as you know, later won the Nobel Prize, at NIH and I said, “Maybe I could take that course and do something with it.”

So he said, “Well, come up and see me,” and I did, and he was absolutely gracious.

I mean, he said, “Well, have you ever dealt with students?”

“Yes.”

He said, “Well, then, you know how they’ll always harass you.”

“Yes, yes.”

“Okay. What textbook do you want to use?” and I suggested a textbook. He said, “You’ll find that’s a little bit too advanced for the students you’ll get here. How about this one?”

I said, “I don’t know that one as well, but fine,” and that was it.

So for four years I taught a two-semester biochemistry course in the evening singlehandedly. And the second semester of the fourth year, through, I think I’d just say a very large administrative mix-up, there were two essentially identical courses being taught in that NIH evening program. And one of them was being taught by a guy who not only was from the Department of Biochemistry at the University of Wisconsin, but who had worked in the same animal room as I did; I mean, his rats and my rats were roommates, in fact. And when we found out about this, we said, “This is utterly stupid.” So, for years thereafter, I would teach one semester and he’d teach the other semester, and this continued with a one-year exception up until 1976, when I knew I wasn’t going to get back from Japan in time to start the semester. So I figured 15 years of teaching, that’s enough. It was a good time to sign off.

Well, then 10 years went by, and I got a phone call that began something like, “You know, we’ve had trouble getting an instructor for introductory biochemistry. Somebody suggested maybe you’d like to teach the course.” For that split second I thought, could I ever rise to this occasion again, and I said no.

“Well, okay. How about teaching half of it?”

A little bit longer pause, “No, I just can’t do it.”

“How about a quarter?”

“Well, yeah, I guess I can do that.”

So I went back into team teaching, you might say, where I taught another 10 years. In any given year, I might teach somewhere between one-third and one-seventh of the course. So I taught introductory biochemistry for 25 years spread over a 35-year period.

And down in the middle, toward the end of the ‘60s, as if I didn’t have enough to do, I found that whereas there were a lot of books available to teach people in introductory chemistry courses how to do the calculations attendant on chemistry, there were essentially none to teach introductory biochemistry students how to do the attendant calculations. So I decided I’d better write one. I can’t believe that I ever had enough energy to do this, because this book was written, I would say, between the hours of 9:30 at night, when the last child got to bed, and 2:00 in the morning. But once I had this book, of course, it was intended to be a supplementary text for people who felt they needed it while they were taking the regular introductory graduate-level biochemistry course. But I also, for several years, taught a course called Mathematical Preparation for the Biochemical Laboratory, so I found lots of ways to keep myself off the streets.

JS: Well, you obviously enjoyed this. You enjoyed the teaching function. It was a nice, I wouldn't say escape from this, but it was a nice addition to what you were doing.

JSF: Well, yes. And, again, I think the FDA got its money's worth out of my moonlighting, and maybe I should talk about the one year that was the exception to my colleague teaching the spring semester when I taught the fall.

He came to me in, I guess it was 1972, in the fall, as I was getting ready to teach mine, and he said, "You know, we're not going to be able to do this next year."

And I said, "Why not?"

And he said, "Well, because I'm going to be taking a year's sabbatical," because he was at NIH, so a year's sabbatical was a normal thing, whereas for me, three months in Japan, that was a great gift. He said, "And so you won't be able to offer the course."

And I said, "Do not fear. I will save your child. I taught this course singlehandedly before, I can teach it singlehandedly again. I'll sit in on your class this coming spring, and then I'll teach it next year, and then when you come back we'll go back to the usual thing."

Well, I did sit in on his classes, and the first thing I came to realize is you can't teach somebody else's course; you have to teach your own course, even if it covers the same material.

So, the other thing I realized is that practically everything in the second semester had changed from the days when I had taught both semesters. I mean, intermediary

metabolism, protein synthesis, nucleic acid synthesis, biochemical genetics, you name it, it had changed.

So, during that year, I literally had to read, cover to cover, the *Journal of Biological Chemistry*, *Proceedings of the National Academy of Sciences*, and *Biochemical Journal* every week. Otherwise, my lectures might be obsolete. I learned and knew more biochemistry during that year than I had ever known before or have ever known since.

Now, typically, in my teaching, about half the students that took the first semester, the fall semester, would either drop out or flunk out, so that by the time my colleague got them, he could just sail along. Well, the same thing happened this year when he wasn't there, but this second semester was like nothing I have ever experienced. We'd start out with something like 45 students. I would put a limit on the class because I figured that was all the papers that I could grade. I started out with about 45 in the fall of 1973. There were some replacements right at the beginning as people decided this wasn't their cup of tea and people on the waiting list would come in.

But the second semester, I had about 23, and it was like having 23 kids, you know, of your own kids, that you had this family of, say, 22-year-olds who were the most dedicated, motivated 22-year-olds that had ever walked the face of the Earth. And we truly became a family, and often we would finish the class and then we'd go down to the North China Restaurant and have supper together. And, as a matter of fact, that year's class had annual class reunions for the next 10 years.

TAPE 2, SIDE A

RT: Well, that became a rewarding experience to you as a professor, then, as well, didn't it.

JSF: Right. And everything is, I think, related. I mean, explaining to a manufacturer in clear and concise and understandable terms why it's necessary to do this, whether it's do this in obedience of the Food, Drug and Cosmetic Act or the Public Health Service Act or the Code of Federal Regulations or just because, if you don't do this, you're violating a fundamental law of science, is not all that different from teaching a class. It is essential to communicate concisely and clearly, and I think this is very important, to do so within the realm of experience of the listener. It is, I think, a necessary thing, and I think whether you're doing it in the classroom or whether you're doing it out on inspection or whether you're doing it in an across-the-table meeting with the manufacturer doesn't really matter. The same requirements are there.

JS: I sort of want to go back to your position after you moved into management and had been there for a few years, obviously, because that's the point you go to Japan. But you became chief of the Laboratory of Plasma Derivatives, first, and later, the Laboratory of Hepatitis -- and we'll talk about the second position in particular in a moment. But I'm curious: were you having more interactions with management of the Center or of the Bureau, sort of concomitant with the change in position in the organization?

JSF: Yes. Yes, I definitely was, and how much of this was just simply because of the

position I was in and how much was because we had some very nice crises arise, and how much was because of the turnover at the level that would be immediately above mine, I don't know. It's hard to sort this all out. And maybe expressing it in general terms here is too esoteric.

Soon after we became FDA . . . Well, I should say, at the moment that we became FDA, became the Bureau of Biologics of the FDA, were no longer the Division of Biologics Standards of the NIH, we had a new leader. That was Hank Meyer, Harry Meyer.

JS: And whom had he succeeded?

JSF: He had succeeded Roderick Murray. And Roderick Murray had, with the exception of perhaps a couple of months just while the Division of Biologics Standards was getting itself off the ground in 1955, Dr. Murray had been the only director for its 17 years of existence. I mean, this is just, I think, extraordinary at that level in a regulatory agency. Of course, I'd say he served well, except that the last crisis was the one that got him.

Anyway, Hank Meyer came in, and he began to look around at what was going on in the various divisions under him, and he became quite dissatisfied with the Division of Blood and Blood Products. And so he . . . Well, he kept his own counsel. I mean, I know why I would have been dissatisfied, and I guess I can speak of the man without fear of libel because both he and his wife are dead. But this is the man I talked of before who had been at the cutting edge of the development of the science which underlay the entire

plasma-derivatives industry, but he had lost interest in science and decided to be a manager, except he was an utterly atrocious manager. I mean, his efficiency of working was probably close to a hundred percent, but his total work output was so close to the baseline, it was almost undetectable. Things would sit on his desk for essentially infinity, and he might sign something, and then he would always fail to follow it up and then deny that he had ever signed it in the first place. I mean, I don't know why Hank Meyer got disillusioned, but I was there first anyway.

And so Hank Meyer decided to bring in Lew Barker, who had been a Branch Director in the Division of Virology. And Lou Barker said, in effect, "Sure, I'll take the job if I can bring my whole branch with me and transport it from Virology into Blood." And that's how Blood got the Hepatitis Branch. Previous to that, it had been in Virology. And Lew Barker was an extraordinarily bright guy.

But not too terribly long after a real FDA type crisis, which we should probably talk about, Lew Barker was offered and decided to accept the job as Medical Director of the American Red Cross. Well, of course, as soon as he made that announcement, he couldn't do any regulation which impacted on the Red Cross. Well, the Red Cross traditionally has been responsible for, in round numbers, half of the American blood supply, so in effect what that meant was that his deputy had to take over all of those duties, and his deputy at that time was Joel Solomon.

Well, when Lew Barker actually formally left, there was a recruitment action for the directorship, but for a long, long period of time, Joel Solomon was in an Acting capacity, which meant that he didn't quite have the authority that a permanent director would have, and very often things would arise that he didn't have the technical expertise

for, so I was being called to interact directly with Dr. Meyer quite frequently over this period. And there were some periods even later than that where, for a given time, we wouldn't even have an acting head of Blood at all. So each of the Branch Directors would have to interact with the Bureau Director. I mean, this didn't last very long, but . . .

JS: Well, this is all taking place, as you said, in the face of crises.

JSF: Crises, yes.

JS: Can you talk a little bit about that? I want to talk about those.

JSF: Yes, I should talk about that because I think it's illustrative of many things. And, again, I'm setting the stage in very general terms here, which probably are basically meaningless.

Two of the plasma derivatives that were prepared in great abundance and used clinically in much greater abundance than they should have been, were albumin and one called plasma protein fraction, which is an albumin-rich 5% protein solution, but it's just less pure than albumin. Albumin must constitute at least 83 percent of it, but it was heterogeneous and less heat-stable than albumin.

It's a product that still exists, but in my opinion and that of many clinicians, has long since outlived its usefulness. It was created at a time before there was no source, so plasma was sort of a rare national resource, if you will, and people were trying to figure

out some way to make something that would be as safe as albumin -- safe in those days meant free from the transmission of hepatitis B -- but was simpler and cheaper to make and would conserve plasma. In other words, you'd get a better yield of it than you would get of albumin.

Is that clear?

JS: That's clear. Could you say something about what you're using it for?

JSF: Well, plasma protein fraction was used therapeutically the same way that 5% albumin had been used. In other words, it was used as a resuscitation fluid.

Now, in the interests of truth in packaging, I've got to say that this all emerged, I think, from the time of World War II, when albumin was first created as a product. And the only albumin in those days was a 25 percent solution. And Isadore Ravdin came back from Pearl Harbor with these glowing stories of how this was a wonder drug. It just resuscitated soldiers who were at death's door. And there were some clinical studies done that were certainly done by people with good will and good intelligence but would never pass muster as controlled clinical trials today. But that sort of put the cap on it in that albumin was a great thing, because people believed, as they had believed in World War I, that if you had a trauma situation with massive loss of blood and so forth and you couldn't replace it with blood, which of course you couldn't because the whole blood bank business hadn't gotten off the ground yet, that you had to use some kind of a colloid, some kind of macromolecule that dissolved in saltwater that would have a water-holding and water-drawing capacity just to keep plasma volume up. So that's why these

things are called plasma volume expanders. Then the nomenclature sort of became a little more elaborate, but that basically is what they were called.

So, anyway, after much working around, finally somebody with the Cutter Company came up with a way that you could go most of the way through the Cohn fractionation scheme and then just sort of do one step and precipitate all the remaining protein as one fraction. And that was called plasma protein fraction. And it could be bottled up as a 5 percent protein solution, of which at least 83 percent had to be albumin, and this could be heated for 10 hours at 60 degrees Celsius in the presence of stabilizers, just as 5 percent albumin was, and that was known to kill the hepatitis B virus.

So, now, this was licensed in 1958. It was licensed two weeks before I came on board, so I say I'm not responsible for that.

The Korean War was fought with the medical corps having pretty much the same mindset that they had during World War II, in other words, that you had to have a colloid there, you had to have a macromolecule solution for resuscitation. At least they weren't using dried pooled plasma, which had been widely used in World War II, which may have been effective in resuscitating people. It certainly was effective in transmitting hepatitis B.

But by the time Vietnam came along, two things happened: rapid evacuation and the realization that you didn't need a colloid. Saltwater and red blood cells were all you needed, and if you could evacuate somebody within 20 minutes, you probably didn't need either, because once you got back to the field hospital, then you could figure out the mixture of red blood cells and saltwater to use.

So this plasma protein fraction continued to be marketed and continued to be used, especially by surgeons, especially by trauma surgeons, but, in my opinion, had sort of outlived its real usefulness. But it's still on the market today. There's really, I think, only one company that makes an 85 percent albumin plasma protein fraction.

But, nonetheless, it is usually monitored, unless you have some really fancy equipment and you can hook the patient up to it, by saying, "Oh, well, the patient's been bleeding a lot; therefore, the patient's blood pressure has dropped. You administer this solution and check to see if the blood pressure is rising toward normal." It's a pretty standard medical practice.

Well, during the spring of 1977, we began getting reports that plasma protein fraction was causing hypotensive episodes. Now, if there's something that you monitor by seeing how much it raises the blood pressure, and it's lowering the blood pressure, you've got a big problem there. We had received quite sporadic reports of this in the past. I'd only been in plasma derivatives for less than two years, approaching two years at the time, but I learned that sporadic reports had been received and people tried to do various pharmacological types of experiments using experimental animals to try and figure out what was going on, but it wasn't very clear.

Well, I should say that among the functions that FDA and Biologics in particular had is the educational function. So in February of 1975, we had about a three-day workshop on albumin. And this workshop on albumin, sort of an expanded definition of albumin, took place on the NIH campus, and was highly attended, and the proceedings thereof were published by the Government Printing Office.

And one of the companies decided, from their own investigations and I guess from hearing presentations from this workshop, that there's this stuff called bradykinin that can inhabit biological products, and bradykinin was, and still is as far as I know, the most potent of the physiologically occurring vasodilators. So if you dilate the vessel and have a constant amount of fluid in there, the blood pressure goes down.

Well, they said, "Wow, if we can get rid of this in our product, then we should have a safer product and we can advertise and make this a marketing point. So one of the first things I remember when I became the Branch Director of the Plasma Derivatives Branch was that an application from Cutter for a labeling change came in, and they presented very, very convincing data to show that the bradykinin content of their plasma protein fraction was, lot by lot by lot, less than two nanograms per milliliter. That was really very impressive. And they documented it, so I approved it.

What they didn't bother to tell us was, in order to achieve this, they changed their manufacturing process, which is a gigantic no-no. Now, if they had told us, would I have ever seen the red flags coming up? Who knows. But the point is, they didn't tell us.

In retrospect, their idea of how to get rid of it was utterly ingenious, utterly ingenious. They had said, where does bradykinin come from? This is where I would love to be drawing on the blackboard. But bradykinin is a very, very tiny peptide. The molecular weight is about 1,000. It is clipped out of a very large molecule which circulates in the bloodstream. This very large molecule is called high-molecular-weight kininogen. Two little clips on this thing that has a molecular weight of 120,000 clips out this thing whose molecular weight is barely 1,000, and then it can have this effect of causing vasodilation.

Well, they said, there is no way that you can go through all the steps that you have to go through to manufacture plasma protein fraction and not have bradykinin generated, so let's do something to generate all the bradykinin that can possibly be generated, and then, because it's so small a molecule, we can get rid of it by ultrafiltration, and then we'll be home free. Well, they did. They prepared a product that was essentially free of bradykinin.

The only problem was, in order to generate it, they had to activate the whole so-called contact-activation system, which means now you're back in the blood-clotting arena. What happens is this blood-clotting factor -- we're not going to draw out the whole blood-clotting scheme, but there's factor XII -- which is activated by coming in contact with negatively charged surfaces. It splits in such a way to become active, and then it sets off the blood-clotting cascade.

But that's not the only thing it does. It also reacts with a protein that circulates in the bloodstream called prekallikrein to convert it to the active enzyme, kallikrein. Kallikrein does two things. One, it clips high-molecular-weight kininogen to release bradykinin. It also feeds back and reacts with factor XII to create more active factor XII.

Well, what was happening as all this stuff was going on in the tank? They were making bradykinin, which they could get rid of very nicely, but they were also making a very active derivative of factor XII, which we named  $\beta$ -XIIa. The first thing produced is called  $\alpha$ -XIIa, and this was a small piece of it called  $\beta$ -XIIa, and that was the culprit. That was the thing that was there that they couldn't get rid of by ultrafiltration.

Well, what happened, and why do I say this is important in terms of what I did?

We had to figure out, like *now*, what's going on, and this sure sounds like bradykinin, but they've gotten rid of the bradykinin. What could it be?

Well, it turns out a colleague of mine from graduate school, who was a postdoc when I was a grad student, had come to NIH quite independently, but our paths had crossed. And in the '60s we had collaborated and been the first, or certainly among the first, to show how blood-clotting factor XIII actually works. It's the only blood-clotting factor which, in its active form, doesn't cause a cleavage of a peptide bond, but creates a peptide bond. In other words, it sort of crosslinks the clot. So we had worked together, and I thought of this guy -- his work on factor XIII, important and fundamental as it was, was only one aspect. He's probably primarily a peptide chemist.

So I immediately went to him and said, "How can I educate myself about what might be going on here?"

He said, "Take this book. I edited it."

So the next thing that happened was Hank Meyer said the same thing he always said in those days when there was a blood crisis. I can't really imitate his Texas or Arkansas twang, but it was sort of, "Finlayson, get on an airplane."

So I got on an airplane with John Pisano's book, and by the time I got to California I had more or less read the whole thing. And the company, which was Cutter, had made some very good inroads in figuring out what havoc they had wrought by trying to do a good thing.

Well, I came back and I said to John Pisano, "My lab is going to have to get into this business of working on the contact-activation system immediately, if not sooner."

I had a very active worker in my lab who had come in 1976, just as I was leaving for Japan, ironically enough. She is now an Institute director at NIH today, although hers is not called institute either, it's called a center, the National Center for Research Resources. Dr. Barbara Alving came to my laboratory explicitly to work on the biosynthesis of fibrinogen, the stuff in blood that clots, because I was in the Coagulation Branch. By the time she arrived, I was not only not in the Coagulation Branch, I was in Plasma Derivatives, but I'd left for Japan. Nonetheless, she got right to work. But as soon as this crisis happened, she completely changed her research to start working on the contact-activation system.

I said, "I'm a greenhorn at this. She has an M.D., she's board certified in internal medicine, she's board certified in hematology, but by no stretch of the imagination is either of us a peptide chemist."

So I went back to John Pisano at NIH -- he was in the National Heart, Lung and Blood Institute -- and I said, "Give me some advice here."

He said, "I've got this number-one postdoc who's over here from Japan. Take him. Have him work in your laboratory as long as you need to to solve this problem."

Now, tell me that that'll happen when we're at White Oak. I mean, that's because I had spent 15 years of fence-mending, you know, not in the exploitive sense, but just because we were colleagues and we each gave the other things on a scientific level that created a win-win situation.

And, sure enough, things went fast enough that I would say, well, that the big recall happened in late May or early June of 1977. I mean, something like 1.2 million grams of protein was recalled, and you multiply that by 20 to get how much product there

was because it was a 5 percent solution, so there was a lot of water surrounding it. By September of 1977, we knew enough about this  $\beta$ -XIIa that we could bring in all the manufacturers, teach them how to assay it, and actually distribute a tentative reference material for it.

So this research that sometimes you hear people say, “Well, NIH does research and FDA regulates,” my opinion, if FDA, or at least at CBER -- maybe I should be more enclosed there -- if CBER doesn’t do its own research, it’s dead. It cannot regulate effectively if it doesn’t have a viable research program. And I think this is one of many, many, many examples. I think of Louis Pasteur’s “Chance favors only the prepared minds” that are willing to do what they know their job is, which is to regulate, but regulate in the very best sense.

So, certainly, immediately we had to get that stuff off the market. Then, later on, we had to figure out what, if anything, they could do to, I hesitate to use the word recondition, but that’s a good FDA word, get the stuff back on the market, and at the same time to make sure . . .

#### TAPE 2, SIDE B

JSF: . . . to make sure that other companies weren’t going to get into the same predicament, not deliberately, but just by virtue of the way things happen.

JS: That’s not always an easy sell for people that control our purse strings, though, is it?

JSF: I think not, and that's why, in my opinion, you're better off the fewer political appointees you have up the chain of command.

JS: In terms of the people like on the Hill that control our budget, maybe, again, education is the best tool there to show that research is not just an endeavor done sort of in an ivory tower, but it's also something that's crucial to a public health function.

JSF: Right. I mean, yes, that's right, it's not just for the entertainment of the scientist.

And, well, one of the classic statements made was when a new NIH institute was going to be created. I'm trying to think; it just passed its something like thirtieth anniversary or something, the National Institute of General Medical Sciences. And when whoever it was that was pushing this -- I don't know whether it was the Director of NIH or a scientific director or associate director of research or who it was that was trying to be the driving force behind this -- was talked to by sort of an old Washington hand, and the old Washington hand said to him, "Are you out of your mind? This is never going to fly. No senator ever died of a General Medical Science."

JS: That's true.

JSF: I mean, yes, I think education is very important, but that's the level at which one has to educate.

JS: That's true, and I'm sure there's no coincidence that many of the buildings on the NIH campus are not named after great scientists necessarily.

Just to bring the story of this crisis that you were talking about in full circle, I was just curious, were there injuries associated? Was this product actually released before this recall?

JSF: Oh, yes, yes.

JS: There were injuries associated with this.

JSF: We never got anybody to say that anybody had actually died as a result of this, but there were certainly many episodes where there were some really touch-and-go moments in a variety of settings, which I will get to because I think this is important too, in ICU's or in post-recovery or in operating rooms.

Just to give you an idea how potent this  $\beta$ -XIIa molecule is in setting off this chain of events, which eventually ends up with bradykinin being released. And, of course, it's being released in the patient where it'll do the most harm, so it's not bradykinin in the bottle. It's bradykinin being generated in the patient as a result of this cascade.

One thing we found was that these reactions were very much dependent on the rate at which the product was administered. In other words, the faster the product was administered, the worse the hypotensive event was. Well, perfectly understandable

because if you're monitoring blood pressure and blood pressure's going down, you say, "Oh, the patient isn't responding. Pump this stuff in faster." It goes down some more and the cycle goes on.

The other thing is, of course, if you're using something as a resuscitative fluid, by definition you should be giving it quickly because you're trying to replenish fluid that's been lost, usually by bleeding.

If the solution is being administered rapidly, as rapidly as one would normally administer a resuscitation fluid, if that solution has nine nanograms of  $\beta$ -XIIa per milliliter in it, it can cause a hypotensive episode. If it has 25 or 26 nanograms per milliliter, it can cause total circulatory collapse. That's where you detect the blood pressure at zero. Now, you can't maintain a blood pressure of zero very long and live. As we say this, nobody would ever go on record and say anybody died. But, as they say, there were some really touch-and-go moments which we did document.

The first thought that people had was, well, this is only going to be a problem for people who are on heart-lung bypass. In other words, where you have extracorporeal circulation where an operation is going to be conducted on the heart and/or the lungs, because the lung is the main organ in the body that deactivates bradykinin. It takes a couple of snips that render it no longer an effective vasodilator. And when the lung is working, one pass of the blood through the lungs probably inactivates at least 85 percent of the bradykinin that was in the blood entering the lung circulation.

And so people said, "Well, when you take the lung out of the patient's circulation," which is what, of course, happens when you're on cardiopulmonary bypass, "that's going to be the only time that this is a problem."

Not so, because it turns out, if you're administering this product as rapidly as you think you should be administering it, what you're doing is you're just swamping out all the inhibitory activity that the body might have to inhibit not only bradykinin, but its natural precursor up the line and the next precursor before that.

So among the things that we put into the labeling for plasma protein fraction is this product should under no conditions be administered faster than 10 milliliters per minute. Well, a resuscitative fluid that you can't administer any faster than that is only going to be useful for resuscitation under an extremely narrow range of circumstances. That doesn't mean that physicians, of course, will read the labeling or will follow it, but that was among the responses that we took.

I should also say by way of follow-up to this education activity, six months to the day after that workshop that I told you about where we brought manufacturers in and taught them how to assay this and issued them a tentative reference material, we brought them back in. This was done so that they could share with us and with each other the success that they had had in setting up this assay, what improvements in the assay they had been able to make, what improvements we had been able to make, and what problems they had run into that were going to be in need of correction.

Research isn't something that you do now and you write a paper and you go home and take a nap. I mean, it just has to keep on.

JS: Of course.

That story illustrates so many things about the different ways of carrying out enforcement of the law that you're charged to do.

JSF: Right.

JS: There are many different ways you can do that.

JSF: And I might say that this set off a very long program of research in my lab. It sounds paternalistic to say “my lab,” because I was the only one that wasn’t doing any hands-on experiments. But we got into the contact-activation system in a very big way. As I say, there are all these things that start out being proteins that you think of in terms of blood clotting that were wreaking havoc in plasma volume expanders.

And then one day -- I don’t know whether I was the one that thought of it or Dr. Alving was the one that thought of it. Or maybe it was like the Wright brothers, you know, you say, “Who thought of the second wing on the airplane?” Well, probably it was two minds with a single thought. I said, “Hey, I wonder if these contact-activation factors might be in some of our other products that are used for purposes other than plasma volume expansion. Yes, maybe we ought to look in the immune globulins,” in other words, the antibody-supplying products.

Our primary problem with those over the years, which I had been working on since the ‘60s, was the stability; what could we do to make more-stable product, what could we do to predict the stability of products, and so forth. Now we said, “Let’s get a bunch of different lots, taking some of these retention samples and looking at them.” And it was fantastic because we found levels of these contact-activation factors ranging from almost none to extraordinarily high levels present in the immune globulin. And the

particular pattern of which proteins -- of course, I'm saying this in one minute, but it took years to work out -- the particular pattern of which were high, which were low, was almost a fingerprint for a given company. And thus a company would not only make a consistent product from year to year, but it would have consistent biocontaminants, if you can call it that, from year to year. And, furthermore, it turned out that some of these were probably important in setting off reactions that ultimately ended in the generation of the enzyme that was snipping up the immunoglobulin itself and causing the instability that we'd been chasing over these years. And this is a very good example of our seeing more of the elephant, because, obviously, I didn't just read that one book; I started reading a lot of papers.

And I would say that, oh, yes, kallikrein was one of the things that I mentioned that works to snip bradykinin out of high-molecular-weight kininogen, but which can also feed back and activate more of coagulation factor XII. Yes, yes, it will work, academic researchers were saying, it will work on plasminogen, the precursor of the enzyme that is presumably formed in our blood to dissolve clots so that once we have a clot, it doesn't stay there forever. But it is a sufficiently nonspecific proteolytic enzyme that it will cleave many proteins, including immunoglobulins, as they became known, also, in the '60s, and plasmin is sort of the proximal cause of instability. They would say, "Well, kallikrein, yeah, will activate that precursor, but it's a very, very sluggish activator, so you really don't have to consider it when you talk about contact activation."

Well, consider the average biochemist working on an enzyme experiment. How long does that experiment take? If it's a long experiment, it takes three hours; if it's a short experiment, it takes a few minutes, let's say an average of an hour. Okay.

Now, you take a product and you give it a three-year shelf life. A sluggish enzyme can do an awful lot of damage in three years. So we eventually came to see that this could be a very important thing for one enzyme setting off another, setting off another, and ending up with something that chews up your actual antibody.

JS: Well, did you eventually issue a regulation or a change in the way products like the globulins are manufactured to prevent this sort of thing from happening?

JSF: I think we achieved the same thing, but not with a regulation, because during this time, among the educational things that we did, is at the end of the 1970s, in 1979, we had a very large workshop on immune globulins, immunoglobulins for intravenous application. Now, this in itself caused a little consternation on the part of our colleagues in CDER because they said, “We generally don’t allow a route of administration to be made part of the proper name of a product,” that is, a regulated product.

And we said, “Sports fans, this is not just taking the same product and squirting it into the veins instead of into the muscle. This is a result of 40 years of hard labor on both sides of the Atlantic Ocean to try and make a product that you can put into the veins and doesn’t cause acute vasovagal reactions.”

See, I’ve got to go back into the history of the clinical development of plasma derivatives.

Albumin came along, you took blood out of the veins, you separated the plasma, you went through the Cohn procedure. Of course, the Cohn procedure itself had to evolve. And then you purified the albumin. The albumin you put in solution, and you

did the pharmaceutical finishing steps. You put it back into the vein. Beautiful.

Everybody was happy.

So they said, "Let's move on to the next product."

Well, there were some clotting products which sort of had their day and left. But very soon after that, when John Enders, who later got the Nobel Prize, but not for this, began looking at some of the fractions that Professor Cohn made, said, "Hey, these are full of very viable antibodies." They said, "How can we purify the various immunoglobulins," immunoglobulin G specifically, "out of this?" and eventually it was done.

And then they said, "Okay, well, hey, we've got these kids with measles. Let's squirt it into them because there are plenty of antibodies specifically directed against measles," you know, because practically all your blood donors had had measles as children themselves. So they put it in, intravenously, and these kids started having terrible reactions.

Now, you say, what was the cause of the reaction? It was probably a whole range of things. But their immediate response was very good. These clinicians who were tied to Cohn's group said, "Okay. What we're going to do is every lot of this that's made here at Professor Cohn's pilot plant, we're going to test on ourselves before we ever give it to a patient, and we'll rotate." You know, one would get this lot, the next one would get that lot.

And they said, "Oh, but Professor Janeway," who was the number-one clinical guy, Professor Charles Janeway, Sr., because there was a Charles Janeway, Jr., who was

also a distinguished immunologist -- both of them are now dead, both senior and junior --  
“you’re the chief. You don’t have to participate.”

“No, no,” he said, “I’ll take my turn just like everybody else.”

Well, when it came to be his turn, he almost died. And from that moment on, this label was put on, “Not to be administered intravenously,” or “For intramuscular administration only,” or some equivalent statement. And that lasted for something like 40 years for this particular line of product. In other words, immune globulin human is a product that is not to be administered intravenously, we feel, on this side of the ocean, under any circumstances. But it took a lot of work, research and development, before people figured out how to make something that had the same active ingredient but was safe to administer intravenously. And so immune globulin intravenous human represented not just a different route of administration; it was a whole new product.

JS: Well, route of administration can be very different. We do label things as, say, ophthalmic as a route.

JSF: Yeah.

Anyway, needless to say, what the companies did evolved just as our understanding evolved.

I mean, the first things that were tried, especially by Europeans making product for distribution in Europe, was they said, “Well, let’s fractionate, just in the same way we make the stuff for intramuscular use, and then let’s treat it some way to make it safe for intravenous administration.” And the first thing they thought of was, “Well, we’ll treat it

with pepsin and sort of chew it up a little bit,” because that’s exactly what had been done with the animal-derived antitoxins, and, sure enough, the adverse reactions didn’t go away, but they did become less frequent when that was done.

Well, the problem was, when you did that, the pieces that you ended up with didn’t stay in circulation very long, so the body didn’t get the benefit of more than 24 hours or so, so that wasn’t very good stuff.

And then people began to say, “Well, maybe we can modify this by tweaking,” and that was moderately successful.

And then people began to get to thinking, “Maybe we could take it through a process so that at least the bad things that we know about -- and we were learning about these all the time from our research and manufacturing research -- so that they never make it into the bottle in the first place.

So all this sort of came about, and one of the things that, in terms of stability, that people figured out was that this chewing-up of the immunoglobulin molecule can be essentially turned off if the pH is low enough. And if you make a product of low pH but that has very low buffering capacity, it can be administered intravenously without problems, because the blood’s buffering system will adjust the pH right there in the bloodstream to what it should be. But all this time that the stuff in the bottle, it’s not decomposing because these enzymes are held in abeyance.

So all of these things came about in a stepwise manner. But I think there is this contribution of our lab and the contribution of the industrial labs, and as long as each felt that the other wasn’t trying to con them, I think it was not bad to be collegial.

JS: What was the chance that many academic laboratories were going to take a strong interest in this and invest their time and effort in this? I mean, is this the sort of thing that you would really only see in a lab like ours or in industry?

JSF: Well, I think there are several aspects of this. I mean, certainly an academic lab might work on the same protein and might even work on the same activity of the same protein, but their interest is going to be primarily and simply in elucidating a mechanism, and that's it. I mean, that's a perfectly legitimate academic end in itself.

Our end is, of course, we want to know the mechanism, but we want to know the mechanism so that we can -- and then there will be many blanks to fill in after that -- so that we can know if the manufacturer is pulling our leg; so that we can develop a control test; so that we can evaluate the manufacturer's control test; so that we can offer advice on how to make a more stable product, etc., etc., etc.

I think that's a very good point, that there are some things that just are not going to be of central interest to academic researchers, or even to many NIH researchers, for that matter.

The second thing is, unless the industrial lab goes really out of its way to evaluate its competitors' products, it may become very sophisticated in developing cutting-edge ways to examine its own product. But we have access to all of them, or at least we should have access to all of them. And so we can see these wrinkles, some of which are wrinkles that are generic to a whole product line and some of which seem to be specific and clustering to one set of products.

I'd really love to tell you a story of how Blood was able to help out some other folks, because I think it indicates how it's not only important to communicate with the manufacturers and our NIH colleagues, it's important to communicate within CBER.

A number of years ago -- it was in the '80s -- the people in Vaccines began to receive reports of allergic reactions to rabies vaccine. Now, rabies vaccine can be administered in each of two modes. One is so-called post-exposure prophylaxis -- you're bitten by a dog that's rabid or you have reason to suspect it is rabid, and you start the series. And if you really know the dog is rabid, probably you give rabies immune globulin and start the vaccine series after that.

On the other hand, you could have people who have not been bitten but are in positions where they might be bitten or scratched or lacerated or something; in other words, veterinarians or veterinary students or zookeepers or such people. You would want to have them have an immunity before the event.

Well, when they looked at the epidemiology, they saw that these were the people who were having the allergic reactions. They said, "Oh, yes, well, sure. It makes sense because they have to be boosted every now and then, so, yeah, there's going to be a certain percentage of people who will suffer an allergic reaction when they've been taken through the whole immunization procedure and then boosted periodically after that."

But then they started looking at that. They saw that some companies' products were being overrepresented, shall we say, in these allergic reactions, and some companies had had hardly any at all. "Well," you say, "it's not such a big deal either. Different companies may make a product in vastly different ways." Except here, everybody did almost exactly the same thing to make the product. In other words, you have to grow up

the virus. Okay. Well, you have to grow it out on some kind of cell substrate. Virtually every company used exactly the same cell substrate that had been developed at a research institute. I guess it was the Wistar Institute.

Another thing you have to do is you have to kill the virus. I mean, yeah, Louis Pasteur made a live rabies vaccine, but that was the only game in town in Louis Pasteur's day. Now you probably wouldn't even think of it, and you want that virus to be dead, very dead.

The other thing is, in the course of killing the virus, you want the antigen to be stable so that it will be a good immunogen when you put it in. Okay. Well, how are you going to kill it, kill the virus so you make sure it's dead? Most everybody -- I won't say everybody -- all manufacturers used the same chemical to kill it, beta-propiolactone. Beta-propiolactone is a very simple chemical that is an active acylating agent, and it is a fantastically active alkylating agent; I mean, it's like gangbusters. And, after that, it hydrolyzes and it's gone, so the excess is very easy to get rid of. Okay.

Now, how are we going to stabilize it? What's a good physiological stabilizer? Good old albumin. You can buy it off the shelf. It's been cooked at 60 degrees Celsius for 10 hours and it's very safe from transmitting any bloodborne viruses, so that's good. So, here we are.

The companies all grow up the rabies virus in the same cell substrate.

TAPE 3, SIDE A

JSF: They all killed it with beta-propiolactone, and they all stabilized it with albumin. But there were still these vast differences in the number of allergic-reaction reports.

It turns out the only difference was the sequence in which people, manufacturers, performed these steps, and it was the ones who put in the stabilizer before the killer that got it in trouble. And so when they came to ask the blood people, “Hey, can you shed any light on this?” we said, “Well, what does beta-propiolactone do to albumin?” And the answer is, it alkylates it very nicely. And so they could show that, depending on how much beta-propiolactone per how much albumin you mixed, you could actually create a gradation of how heavily it was alkylated. And with our friends in the allergy section of the Division of Bacterial Products, we were able to show that this alkylated albumin was a very wonderful allergenic agent. And in fact you could make stuff in the test tube by reacting beta-propiolactone and albumin that would react very nicely with the IgE in these patients’ or these veterinarians’ blood.

JS: So the issue here was one of creating an allergenic agent from the albumin, not one of incompletely killing the virus. Right?

JSF: Exactly.

Well, you see, if people hadn’t communicated with each other, this would have been a terrible dilemma for any one group. But by virtue of people communicating and working together, it was solved in a matter of a few months.

JS: Obviously, in situations like this, communication is incredibly important, no doubt about it.

I sort of wanted to move ahead to another period. You mentioned some communications with CDER on an issue of labeling. That reminded me that Biologics and Drugs became one and the same after Dr. (J. Richard) Crout, who was head of the Bureau of Drugs, left. I think there was a problem in finding a replacement for Dr. Crout. This was, oh, gosh, I want to say around 1980, late '70s, around 1980 or so.

JSF: Yes. The melding, I think, happened in '82.

JS: Okay. Because he talks about this problem in his oral history, and, unfortunately, we never were able to sit down with Dr. Meyer. But then, obviously, the Commissioner at the time approaches Dr. Meyer . . .

JSF: Arthur Hull Hayes.

JS: It would have been, yes, it would have been Arthur Hull Hayes, Commissioner Hayes. And I guess convinces Dr. Meyer to take on the function, and I believe he does this on the condition . . . I want you to correct me here.

JSF: You're absolutely right. And I've always wondered if Dr. Meyer hadn't taken a page from Dr. Barker's book when Dr. Barker said, "Yes, I will move from the Division

of Virology into the Division of Blood and Blood Products if I can bring my whole section with me.” Dr. Meyer said, “I will take the job as being head of the Bureau of Drugs if I can bring the entirety of Biologics with me.” So, yes, at that point there was created what was called the National Center for Drugs and Biologics.

Well, I think any regulatory agency in the developed world would have predicted that this would be a failure because every place that I have ever visited, be it England or, I should say the United Kingdom, France, Germany, Switzerland, anyplace that has highly developed regulation of pharmaceutical products, there is always this tension between pharmaceuticals and the biologics. I think it grows out of the history, because the biologics always emerge from sort of the handcrafted, whereas the pharmaceuticals, in principle, can be mass produced. Now, that doesn't mean biologicals can't be produced on a large scale. However, they always seem to grow out of this hovering process, and the feeling is that the regulation should be hovered over in the same way, whereas the feeling in drugs is we can correct these problems in a generic way, then we can keep them from recurring in a generic way. And so this seems to create this tension that is just pervasive. I may have not explained the etiology completely, but it certainly exists.

JS: But this is not an uncommon sense, based on your perceptions, in other countries.

JSF: Right. Well, several amusing things happened.

About a year went by, and somebody of a legal bent uncovered something that said you can't call yourself a national center for anything without a congressional

mandate, and I guess Dr. Meyer said, “No problem, we’ll just knock the national off and call us the Center for Drugs and Biologics.

Well, I mean, all these manipulations, most of which didn’t really affect me one way or the other except the question of, well, who am I reporting to this week, you know, went along.

But it turned out that some functions were just so separate that there was no point going up the whole chain-of-command to the Center Director’s office. So the original OBRR was not the Office of Blood Research and Review, but the Office of Biologics Research and Review, which was an office under this Center for Drugs and Biologics to allow things that were purely biologics in nature to be handled there more expeditiously without having to go up the line. But I guess, finally, by 1988, by which time Dr. Meyer had retired and Dr.(Paul) Parkman was in, it was realized that this isn’t going to work, sports fans, and so we should just get a divorce and make a clean slate of it.

Now, what was interesting was that, in the hopes that it was going to work in the early days, a number of functions had been combined. For example, epidemiology and statistics people had been sort of sliced out of Biologics and put into Drugs. Now they had to get them back so that we would have people who could focus on biologics. And there were administrative people who underwent the same changes. You know, people who arranged travel and so forth and had done the same thing. So it was a strange pathway.

What was so ironic was that, you know, I never knew Dr. Hayes personally. I mean, I certainly knew people who not only knew him from FDA, but knew him from medical school. And they said he was just ecstatic over this combining of two bureaus

into a center. And he said, “Well, what else can I combine?” And he took what seemed to be the two most divergent things you could have, I mean, the Bureau of Radiological Health and the Bureau of Medical Devices, and he put these two divergent things together, and they just functioned wonderfully.

JS: Probably no small credit due to John Villforth in that respect.

JSF: Probably.

JS: But those things that irradiate, they must come from some kinds of devices, right?

JSF: Maybe it wasn't all that bad after all. But, I mean, it was so ironic that the inspiration for this didn't work at all, and the derivative functioned quite nicely.

JS: Now, this is an incredible decade when this was all going on, in the 1980s, because, obviously, toward the latter part of the decade, you're now chief of the Laboratory of Hepatitis, and obviously the HIV/AIDS crisis is consuming a huge chunk of the attention of the Center for Biologics, or whatever you want to call the biologics function right now.

JSF: Yes.

JS: How much of that, how much of the HIV/AIDS issues and attention were you focusing on during this time in the 1980s?

JSF: Well, of course, I was aware of the things that were going on in terms of, first, the hemophilia A community and then the hemophilia B community and blood itself. But I was peripheral to all of this because, first, I was no longer in the Coagulation Branch, and, secondly, we had people who were primarily handling the coagulation products. And at least initially, it seemed that the products that I was dealing with were home free, and I'll get to that in a minute because I don't want to jump to there right now.

JS: And I just wanted to add that it's 1986 that your position changes. You become the Chief of the Laboratory of Hepatitis.

JSF: Yes. And I should have put "acting" there, Acting Chief of Hepatitis and, later, Acting Chief of Hemostasis and Thrombosis.

But the first event, the hepatitis, came about in a very strange manner.

At the time, that is, between September of 1985 and September of 1987, the Director of the Division of Blood and Blood Products was Dr. Thomas Zuck, and this was a rather interesting arrangement because he was in the Army Medical Corps, and we rented him from the Army, and several days a week he would actually wear his uniform. Several days he'd wear, I guess it used to be called mufti in the old days.

And Dr. Zuck was a very interesting guy. I mean, he'd done a certain amount of research in the blood world himself. He was an M.D. He also had, I guess, a J.D. He was a very energetic guy. But he had been in the Army Medical Corps for 23 years at the time he came to Biologics. And he had been in the Army for so long that he sort of thought that if he did things the Army way, then they'd just take care of themselves. In other words, he'd say, "Where's your procedural manual?"

"What?"

"Your procedural manual. Don't you have a procedural manual?"

"Well, I suppose we do have one somewhere, maybe up in the Parklawn Building or something."

"No. But, I mean, your SOP's."

But he had this wonderful, almost childlike belief that if you wrote down an SOP, then there would be no situation that would be deviant from that that you would ever encounter, and you could just go there and go down to line 4B and solve it.

Well, of course, everything in Biologics is deviated all the time. That's the nature of the beast.

Well, he also was a very good man at making decisions. I mean, he'd make decisions at the drop of a hat. And, in fact, he tended to make decisions only at the drop of a hat. So the result of this and several other things was that nobody was neutral about Tom Zuck. People either got along with him very nicely, which I did, or they despised him.

Well, anyway, as you know, it was in the spring of 1985 that the first test for what was then called anti-HTLV-III, the name that we used on this side of the ocean when we

talked about the AIDS virus, that the test kits became licensed. And when Dr. Zuck came aboard and sort of got his feet on the ground and so forth, and about of a year had gone by since these tests had first been licensed, he began to worry about the tests that were being performed in Biologics at that time. Now we were not yet called CBER, I guess, because we still were in the Drugs and Biologics mode. He wondered whether the tests that were being performed to release the lots of kits so that blood banks and plasmapheresis centers could use them, whether our testing program really was up to snuff.

And so he asked me and one other person essentially to review all of our in-house test records for the release of these test kits. And so we spent about three weeks, I would say, from dawn to dusk just looking at these columns and columns and columns of little numbers and comparing them with the specifications. What we found was that there was no evidence that kits that were insufficiently sensitive had ever been released, but there were some situations where the positive controls and the negative controls in a given test were not really within what the specifications should have been, and ideally that test should have been repeated. And you wondered, well, why somebody who was sort of looking over the shoulder of the people doing the test didn't pick it up. But, again, when you delved further and further and further into it, it looked like there were enough built-in checkpoints that no lots that were not sufficiently sensitive had ever been released.

So, after that, I was ready to go back to whatever it was I was doing with the Plasma Derivatives folks, and Dr. Zuck said to me, "Now, would you do me just one more favor?"

Well, when the boss says, "Would you do me one more favor?" you either answer "Aye-aye, sir," or "I resign, sir." So I said, "Well, okay. I guess I can do you another favor. What is it?"

He says, "I want you to take over the Laboratory" -- we were called laboratories by this time -- "I want you to take over the Laboratory of Hepatitis."

Well, you know, I'd done a lot of different things in the years up to that point. After all, I was now approaching 30 years in biologics regulation. But I certainly had never done anything in regulating of test kits of any kind, or hepatitis in particular. And I said something like, "Sir, I don't think I really know how to spell hepatitis."

He says, "You'll learn, you'll learn."

So the first thing I knew, beginning around April of 1986, was now I was the Lab Chief of Plasma Derivatives and I was the Acting Lab Chief of the Laboratory of Hepatitis. As I began to look at the testing program there, I could see that there were many things that were analogous to what I had encountered when I had moved into Plasma Derivatives. There were package inserts that were excruciatingly outdated and needed to be, not just tweaked, but massively modified.

There, the tests that were being carried out to release kits under a surveillance program were being carried out competently, but there didn't seem to be any regimen. And certainly, when one would go back in a systematic manner and review the results, some things didn't seem to be there. So, with the aid of one colleague who just willingly gave up his whole research program to help me out (he had been in hepatitis for a long time but I think sort of felt unfulfilled), we got things off the ground and moving.

But about this time, the guy who was essentially acting as my unofficial deputy chief in Plasma Derivatives came to me -- I think we had a conference out at the loading dock, the only place we felt we were not going to be overheard -- and he said, "You know, people are getting very nervous in Plasma Derivatives because they aren't sure who they're supposed to report to. They think they should report to you, but you're chasing after hepatitis problems, and I say, 'Well, you can report to me,' but they don't think I have the authority. What should we do?"

And I said, "This is what we will do. You will be the Chief of Plasma Derivatives from this moment forward, and I will devote myself exclusively to hepatitis." I'm sure that would never stand up to today's scrutiny of our personnel office.

JS: You mean you didn't do a search?

JSF: No. The one thing I can be sure of is that we would never have found anybody better.

But the point is, I then got into hepatitis in a big way, and I think we were able to clean up package inserts, we were able to clean up manufacturers.

In fact, as I mentioned, there was this, it was called a surveillance program. In other words, it's written into the Code of Federal Regulations that if a manufacturer, after licensure, makes five consecutive lots of hepatitis kits that pass, then that manufacturer can request going onto a surveillance program where it doesn't have to submit every lot for lot-by-lot release, but can submit the first lot manufactured every quarter for surveillance testing.

Well, among the things that happened was one company, which is no longer in business, was doing so bad on this surveillance program that we turned it back on to lot-by-lot release. So I think we really tightened up a number of things.

Another thing was, during that time, we were able to recruit a full-time lab chief for the Laboratory of Hepatitis.

Now, you're thinking, well, how did the AIDS thing impact . . .

[tape recorder turned off and on]

JSF: One of the things that happened to me personally in the era of Dr. Zuck, which was a direct effect of AIDS having come along, is that over a considerable span of time, I would get telephone calls referred to me that all began almost the same way. "My wife" or "I" or "My child" or "My patient" or "My client" is going to go off to Timbuktu, and it's been recommended that, for prophylaxis of hepatitis A, I or my wife -- fill in all the blanks -- should get a shot of immune globulin. Am I, is she, is he going to get AIDS from this? Well, of course, at least, nobody knew, and nobody seemed to be willing to take these phone calls except me.

So, the first thing I would say is, "It's important to remember that there has never been a documented transmission of AIDS, or once sensitive testing became available, of any infection by an immune globulin that's licensed by the FDA. If I could tell you why this is so, I'd be glad to do so, but I can't tell you. I can just tell you why I think it's likely to be so."

And then I would say, "The best we can do is to think in analogies with another virus, namely hepatitis B. There has never been a transmission of hepatitis B by an

immune globulin made the way immune globulins are made in the U.S. for licensure. But there was a transmission by an intermediate product that was sold to another country from which it made its own kind of product. When that intermediate material was examined, it was found to be high in the antigen that the virus carries on its surface and very, very low in the antibody to that virus, which made it a far, far outlier. Now, I can't say for sure that that's exactly what's going on with the AIDS virus, but we know that we have never gotten a documented report."

And usually, if you spent time with people, you could sort of feel their anxiety level go down, and then I would always end up with my little speech, which is, "It's like any other medication. If you need it, don't deny yourself it. If you don't need it and it's just sort of casual, for heaven's sake, avoid it; run." I would say I was averaging, for close to a year, about three hours a day of phone conversations like this.

Finally, by early 1986, we had the answer of why this hadn't happened, because of work done by Plasma Derivatives -- that guy who took over in Plasma Derivatives hadn't yet taken over; he still reported to me at this point -- in collaboration with the folks in the Division of Virology.

#### TAPE 3, SIDE B

JSF: In collaboration with the people in Virology, he had designed an experiment to mimic the way manufacturers make plasma derivatives in general and immune globulins in particular. And what they were able to show by a series of spiking experiments, which could be done in the P3 facility with materials that he had prepared so that essentially all

the virologist that was in the facility would have to do was mix and match, and then sample for testing purposes. What they showed was that, first, there was a shunting of the virus away from the product; and the second thing was, the alcohol level that was used to bring about the final precipitation of the immune globulin -- I shouldn't say final - - along the way to the final, that that very nicely inactivated the virus that we call HIV today. And since there are two such steps along the way, it was certain that unequivocally we had our answers. So it was, once again, the fact that you could not only make your most educated guess, which is what I was doing over the phone, but you could actually do the research hands-on and show the results.

Once these two folks had the results, there were probably about a dozen other people who were quite willing to have their name put on the paper when it was published. But, again, it took a lot of communication within CBER.

Now, once this information was available, and once the test for the antibody to what today -- I'll just keep calling it HIV for simplicity, not worrying about what the nomenclature was in those days -- once this test had become valid and been approved over the years, we had an interesting little situation that arose when Desert Shield came about.

Desert Shield, you know, was followed by Desert Storm, where we went into . . .

JS: Kuwait.

JSF: Kuwait, right. Well, for reasons known best to the Saudis, the Saudis made this

rule that everybody coming into Saudi Arabia had to be tested for anti-HIV. And if you were positive, you didn't come across that border. Okay.

Now, let's pause here and think about this. If you're sending American soldiers off to the Middle East, what's one of the things you had better do? You'd better make sure they get their immunizations, including immunization to hepatitis A. The only problem is, in those days there was no hepatitis A vaccine. There was a hepatitis B vaccine but not a hepatitis A vaccine. How do you make sure they are immune to hepatitis A? Passive prophylaxis. You give them immune globulin. Okay.

Well, immune globulin has a three-year shelf life, and so some of it was certainly being made and stored and distributed from plasma that was collected before there was a test for anti-HIV. So, what was the result? There were going to be some donors who were positive for anti-HIV, and their plasma was going to go into the pool that was going to be fractionated, and their antibodies were going to do just what all the other antibodies do. They would precipitate exactly where immunoglobulin G should precipitate, and they were going to show up in the product. That didn't make the product dangerous at all. We had already shown by this time that it was safe, there had never been a documented case, and we now knew why it was safe. But the only thing was, the process for concentrating antibodies concentrated all the antibodies, including those to HIV. So when you injected this into somebody, a certain amount of that found its way into the bloodstream. You tested them, and if they were tested soon enough after having received that immunization, they would test positive.

So, here we had all the soldiers getting immunized, certainly a substantial number of them getting immunized with a product which contained the ready-made antibody to

HIV, causing them to give a positive test, and causing the border guards or whoever they were in Saudi Arabia to freak out.

So this was something on which I was able to collaborate with some folks doing some laboratory testing at CBER. But to sort this out, if you can imagine, this had to go up to the level of the State Department. Just to show you how everything turns out to be related to everything else.

JS: But it did get straightened out.

JSF: It did get straightened out.

JS: It didn't turn out to be an international incident.

JSF: It took some convincing, because Saudi generals don't seem to be any more guiding lights of the intellectual world than American generals, but eventually it was all straightened out. Possibly, Dr. Zuck's tie-in with the Army was useful in that circumstance.

JS: Good, good.

Well, we didn't have a vaccine for hepatitis A. We did eventually have one . . .

JSF: We do now.

JS: We do now.

JSF: Yes. I think about 1995 it got licensed.

JS: Now, what about hepatitis C?

JSF: What about hepatitis C? Okay. That's a good introductory line.

In 1989, it was reported in *Science* that molecular biology had been done. This was not a classic viral isolation. This was isolating part of the genome of the virus and expanding thereupon, so that they could create at that time a limited portion of the protein that the virus elaborates during its replication and could use it to detect an antibody that would recognize that span of peptide. On that basis, they had the beginning of creating test kits to detect people who were carriers of hepatitis C. And hepatitis C had been known as non-A/non-B hepatitis up to that point because there was no specific test for it, so it always had to be a diagnosis of exclusion. It wasn't hepatitis B and you could rule out it wasn't hepatitis A, so it's non-A/non-B by definition. The vast, vast, vast, vast, vast majority of it turned out to be hepatitis C.

They said that, okay, a test should be developed, and by, I believe it was the first of May 1990, the test was licensed. One company was licensed, and then soon after that another, and eventually more. So it was a remarkably rapid development once the fundamental molecular biology had been worked out, and this was not a national crash program like the developing of the test for the AIDS virus had been, where it had all been

under national auspices. This was simply worked out by the manufacturer seeing a good thing and deciding to make use of the fundamental science. So we could already see, by the end of 1989, the beginning of 1990, that blood and blood donors were going to be tested for the antibody to hepatitis C as soon as the test became available.

The thing was, there were these two wild and crazy guys who said, “Yes, but you’d better think twice before you start testing donors of plasma for fractionation to make plasma derivatives for this antibody.” Well, these wild and crazy guys happened to be, one, the fellow who did the experiment to show why immune globulins were safe, and the other one, who happens to be speaking right now. And we said, “Now, look, sports fans, this antibody that you test for when you’re testing to see whether the donor is a carrier of hepatitis C, this antibody develops very slowly.” People gave various figures -- 20 weeks, 28 weeks, whatever -- after the time of the initial exposure until that antibody reached its maximum titer in the bloodstream, and at some point between there was when it first becomes detectable by a test.

And we said, “Now, we don’t know what the natural history of the hepatitis C virus is. It’s too early.” But if it’s like most other viruses circulating in the blood, soon after infection, it replicates very nicely, you get a very high viral titer in the bloodstream, and then it gradually fades off and gets to some sort of chronic level because hepatitis C, non-A/non-B hepatitis, is known to be largely chronic. At least half of the people were in a chronic state, unlike hepatitis B, where maybe 5, 6, 7 percent become chronic carriers.

So we said, “What does this mean?” What this means is that you have a very good chance, if you’re going to get tested out here for the antibody -- you’re not testing for the virus; you’re testing for the antibody. If you test for the antibody and discard the

positive units of plasma, you may be keeping the ones with the high viral titer in and disposing of those with the low viral titer. And, furthermore, you don't know whether there are antibodies that circulate along with the antibody that your test detects that may be beneficial antibodies. And these beneficial antibodies don't necessarily have to neutralize the virus, although some of them may do so. If they simply interact with the virus to shift the virus away from the protein that you're going to put into the product, they can still be beneficial.

Well, this set off a firestorm, and there was a lot of controversy. I mean, we weren't saying don't test the blood donors, because, obviously, blood is transfused one unit at a time. So if you have an infectious unit and you take it out, you've done something. If you don't detect 100 percent, well, no big deal because if you have gotten rid of those that you would have transfused as blood or as a blood component made at a blood bank, you've done something. Well, we're talking about plasma that is going to be pooled into large pools. And, of course, we could show mathematically why our argument was extremely sound. The only problem is, many of the leading lights in our scientific community have advanced degrees but can no longer handle ninth grade algebra. So that was sort of a big problem.

Fortunately, we were able to do two things. We were able to convince our management within, I guess it was OBRR with the other meaning, you know, Office of Biologics Research and Review, that we should put the brake on things. We were then able to convince the manufacturers to help us do an experiment.

So what we eventually orchestrated was that plasma centers, some plasma centers whose help we enlisted, would collect on one day a large number of, I think over 3,000

units of plasma. This is Source Plasma, capital S, capital P, you know, all collected by plasmapheresis and to be used only for fractionation into manufactured product. It was all collected on one day. You knew you were not going to get any duplicates, so each donor would be represented only one time. These donors would all be screened by all of the usual tests, except for hepatitis C. They had to pass all those other tests. Then they'd be tested with the licensed test for hepatitis C and we could segregate those into the positive and negative. Then we took the negative units, you know, the ones that were negative, and pooled them. And we took some samples of that, just plasma, and froze that away. Then we took the rest and divided it up and sent it to all the manufacturers licensed to make an intravenous immune globulin product, told them to fractionate it by their own methods, and send us back the immune globulin they made.

So then, what do we have? First we had this anti-HCV-negative plasma, so that we put into chimpanzees. What happened? The chimpanzees got hepatitis C very nicely, thank you, showing that this test, although it was good, could in no way, shape, or form guarantee you a hepatitis C-free plasma pool. The pools were going to be contaminated no matter what because the test just wasn't a hundred percent sensitive. That's the way it was.

Then we took this, these immune globulins that they came back with, combined them so that there was an equal representation of the amount from every manufacturer, put that into other chimpanzees so that every manufacturer was equally represented in every chimpanzee, you know, got the same load, and followed those chimpanzees for a year. So we actually were able to put the brakes on for a year to get this experiment

carried out. Well, I said we put the brakes on for a year, close to a year. I'll modify that in a second. And those chimpanzees never did get hep C.

After we had gotten to about a six- or seven-month point, we said, "It's far enough along. We can be confident of what's going to happen." So we took this to our Blood Products Advisory Committee and we said, "Here are our results. We believe that we can now allow manufacturers to test Source Plasma, plasma for fractionation, plasma for further manufacturing, for this antibody to hepatitis C. And we will not be harmed -- and I'll not list all the reasons -- will not be harmed by withholding those units that come out reactively."

"However," we said, "we also know that more sensitive tests are coming along," because by this time the molecular biology of hepatitis C had advanced quite a bit, so that people could make other peptides and make a more complicated test, so-called multi-antigen test, which would detect more donor units that would be potentially infectious.

We said, "Obviously, when this test comes along, we'll want it to be put into use for blood banks because you'll weed out additional infectious units of blood. On the other hand, we don't know how it's going to shift the balance of plasma that's going to be pooled for fractionation. You will be detecting more infectious donors, but at the same time, because you have a broader spectrum of antigens to which antibodies can respond, you would have a better chance of pulling out beneficial antibodies." Well, you know, there weren't that many people in the hepatitis-expert world who believed that there were beneficial antibodies, so we were always fighting uphill.

And so we said, "We will put three questions to our Blood Products Advisory Committee." We asked, "Do you believe that we should test plasma for further

manufacturing for anti-HCV? Two, do you believe that units that come up reactive should be withheld from fractionation pools? Three, do you believe that, if you say yes to one and two, do you believe that, concomitant with that, steps should be put in place for viral clearance of all plasma derivatives?" Because at this time, albumin and PPF, of course, had been heated to kill viruses from day one; and beginning in the '80s and moving on, the coagulation factors had all been either been heated or treated some other way to kill viruses. And as other products came along, many of those were treated. But here we had the immune globulins, which at that moment -- now we're talking about September 1991 -- none of the immune globulins was or had ever been deliberately treated to clear viruses.

Well, in my naivete, I thought this was asking them to endorse mother's milk. But how did they vote? Yes, we should test plasma for further manufacturing for anti-hepatitis C; yes, units that are reactive for anti-hepatitis C should be withheld from fractionation pools. No way should anybody in the world begin to require viral clearance for all plasma derivatives. Just absolutely stunning. I mean, they just simply refused to go along with this.

Well, to make a very protracted story very short, in fact brutally short, by January of 1992, we felt so strongly about this that we sent a letter not only to all manufacturers of immune globulin, but all those who had given indications that they intended to develop immune globulins and said, "We think you want to introduce steps that will clear viruses, or, alternatively, if you believe you already have a process to do this, that you should validate those steps which you have." But since this was sort of flying in the face of our

own outside expert advisors, we didn't put a time limit on it, said, "You tell us when you think you're ready to implement such things."

Well, the next thing that is pertinent to this saga is, Washington's birthday is celebrated about this time, right, in 1994. I was getting ready to take a nap since it was a nice Monday and it was peaceful in the afternoon, and my phone rang. And it was, I don't know whether it was the responsible head or one of the other higher-ups at Baxter. And he said, "I'm sorry to bother you at home." He was very diffident. "Sorry to bother you at home, but we called Compliance and nobody answered." Of course not; it was a government holiday, so nobody was in our Compliance Office.

"Yes."

He said, "Well, then I called the FDA hotline, and nobody answered that either, so I'm calling you."

I'm thinking, isn't it nice to be loved.

And then he began to tell me that they were initiating a worldwide withdrawal. There had been -- I don't remember the exact number, but something like eight or nine cases of hepatitis C caused by their immune globulin, intravenous, and many of these had been in Spain, but there had been some other countries. And in retrospect, there may have been a case in the U.S. that had somehow slipped through. But the point was, there was a worldwide withdrawal of this one particular company's immune globulin intravenous.

Fortunately, nobody else, no other company's immune globulin intravenous caused this problem. But at this point, we sort of went into overdrive and said to all manufacturers, "Okay, you respond to this letter in 10 days telling what you're going to

do and laying out a program of how you're going either to validate what you're doing now or that you're going to put into place these steps."

It turned out, after, again, a lot of research on the part of people from the Plasma Derivatives Section, in close connection with those in other parts of OBRR -- now meaning the Office of Blood Research and Review -- that the Baxter Company's margin of safety had just been the thinnest, and simply going from using -- I'll use incorrect terminology but it's simple -- going from first-generation testing kits to second-generation testing kits had been all that was necessary, in effect, to weed out the beneficial antibodies and leave in just enough of the virus to make it all the way through to final product.

As I've said over and over again, I would much rather that our hypothesis and algebra had been wrong than have anybody get sick. But, unfortunately, it didn't turn out that way.

We and the company got busy, so even Baxter was back in business within less than three months. They had initiated and validated a way to kill the virus. But, again, it just shows what can happen.

But we had been, of course, focusing on the stuff that was going to go in intravenously because, first, it would be right there, it would get to the liver right away, and it would be given in large amounts. But we certainly were worrying, at the same time, about the intramuscular materials, for which companies had not yet, for the most part, put any viral clearance steps in.

But in the course of this, one of our investigators in Plasma Derivatives who had been working on hepatitis B safety of products shifted her research all over to hepatitis C.

I should say today she covers the whole waterfront of viral safety. She switched immediately over to hepatitis C, developed a test for detecting the viral RNA, and was able to start applying that test to the intramuscular immune globulins so that we could actually initiate, for a couple of years, a lot-by-lot screening test until those products also came online to have viral-clearance steps.

But I say, research never sleeps.

JS: No, no, it doesn't. I mean, I can recall, when David Kessler was Commissioner, him going to Congress on occasion and trying to argue why this is important, and he did invoke work that Biologics was doing. I'm sure he wasn't the only Commissioner to do that, but it's certainly a good illustration of why that's important.

I think as we move through the '90s and up to 2000, I guess it would be helpful if there's a particular crisis or issue that you can put your finger on that helps sort of identify what are our needs, what we can learn from, what we did learn from in Biologics, and specifically what the agency learned from generally.

Now, I know we've had ongoing problems with some establishments. We can mention this briefly off tape.

[tape recorder turned off and on]

JS: Okay. Well, what we want to proceed with is sort of a look back at the most recent decade or so, or at least since, say, the mid-'90s, 1990s or so. Perhaps there are some events or issues or trends that you think are illustrative of what the agency needs to be doing, maybe what the public needs to know about the agency that perhaps they don't

know and they don't understand. Can you give us an overview of maybe what some of those things might be?

JSF: Well, let me take the one that I perceive to be easier first, which is what does the public need to know that it doesn't know.

You know, there was a very interesting statistic that came out in a meeting that I attended shortly before my retirement, which was in the early days of 2004. That statistic was public recognition. Seventy percent of the people surveyed -- one hopes it was a representative sample -- it certainly was a large sample -- said they had heard of the FDA. Four percent said they had heard of NIH. So, FDA has name recognition. The other figure is often quoted; it was quoted by Kessler both when he was Commissioner and later, that the FDA regulates material that accounts for 25 cents out of every dollar that the American public spends. Well, we certainly don't have a quarter of the government employees, so the question is, what should be and what realistically can be the function of FDA?

I have become a little bit jaundiced about not only hepatitis over the years, but also what seems to be really important to Congress and to certain executive administrations. It is that there be a perception that there is an FDA, but what you'd really like to have is an FDA that is highly perceived but doesn't do a blessed thing. That way it won't interfere with trade and commerce and industry and all these wonderful people who could devote themselves to getting reelected. And so, everything being tied to everything, I can't really see how one cures the fundamental problems of FDA until two things happen. One is when there is public funding of national elections, and this is

not the time to bring that up in the current economy; and, secondly, when you stop having political appointees running the FDA. Because as long as you have political appointees heading the FDA, it's going to be a political football, and that's just the way life is.

Now, there have been some, I think, very admirable Commissioners. Almost immediately after the conclusion of the interview, and again while reading the transcript, I realized that in mentioning several Commissioners (Jere Goyan, Arthur Hull Hayes, Donald Kennedy, David Kessler, Alexander Schmidt, Frank Young), I had failed to include one recent, and very important, person. That Commissioner is Jane Henney, whose tenure was from January 1999 to January 2001.

The first thing I noticed about Jane Henney was her apparently infinite attention span. Whether a meeting was taking place virtually at dawn or at the end of a long and (for the rest of us) exhausting day, Jane was listening with rapt attention, was composed, and was totally focused. Later, I found her to be an astute observer and decision-maker.

In addition, she was the first female Commissioner. When CBER underwent a major reorganization in 1992-1993, Kathy Zoon became the first female Director in Biologics' 90-year history. I am sure that the support Jane Henney gave to Kathy was highly influential in sustaining the new organization. In my opinion, this stemmed from the fact that Dr. Henney was not only an outstanding Commissioner and a good doctor, she is simply a very good human being. So the mere fact that someone is a political appointee doesn't mean that he or she is not somebody with a heart and brains in the right place, but it's just simply that they are going to be answering to a higher power, and that higher power, let's face it, has one main goal, and that's to get reelected. I mean, like

they would know what a proteolytic enzyme is, let alone care. I mean, that's just not going to happen.

Now, let's -- as I say this, I think of a guy who was done in by Chilean grapes, Frank Young. Frank Young sat at a table right in this building, looking at polyacrylamide gels and knew exactly what those gels were telling.

Now, his deputy turned to me and said, "What's this technique?" and I said, "It's isoelectric focusing of proteins."

He says to me, "Proteins? Are those organic compounds?"

And I'm thinking, "Oh, the country's in good hands."

I will not name who that was.

But, as I say, there have been some just outstanding Commissioners, and probably for a certain amount of time, I just saw the Commissioner as a figurehead that had no interaction at all.

The first one with whom I had interactions was Donald Kennedy, and he was the one who was always catching flak for not being a real doctor. He was a Ph.D. in neuroscience. The guy was absolutely brilliant. Not only was he smooth as silk in public speaking, but this guy was just brilliant. And he would show up in your lab. He would show up in your lab and he would ask questions like a second-year postdoc would ask. I mean, he absolutely understood exactly what you were doing and why you were doing it. And, in fact, some of his questions were so brilliant, I thought, "Damn, why didn't I think of that first?"

However, his subsequent experience at Stanford showed even he could get himself into trouble. He was always put up as the antithesis of Alexander Schmidt, who

spoke very slowly and thoughtfully and was sort of regarded as a pedant. But I thought he was a pretty good guy, and he sort of had a twinkly sense of humor. He described how he was first approached to become Commissioner, and he had said to himself, “Well, it can’t be worse than being dean of a medical school.” And he stopped and grinned and said, “But you know, it is.”

And then, after Kennedy, there were, as we mentioned, Arthur Hull Hayes and Jere Goyan. The only time I ever saw either of these gentlemen was looking out the window as they’d come into the building to talk to Dr. Meyer and then go back and get into their limousine and drive off. So, I mean, about the other end of the world from Donald Kennedy.

Now, David Kessler, I saw quite a bit of, but by this time I was in management, if you will. I was going off to management retreats, management go-aways. I always wondered what would happen if a head of management could stay away. Would the worker-bees really be any worse off? But that’s another story, I guess, for another day.

David Kessler must be a very smart guy. Anybody that can go to medical school and law school at the same time has to have lots of smarts. And anybody that can do his next thing, doing a residency and a congressional internship at the same time, must have had a marvelous ability to discipline himself.

But he had one crusade, which was user fees, the PDUFA Act. He really put his heart and soul behind that, and he knew how to get it through Congress. And the philosophy was, well, these industries are getting the benefit of, from Biologics’ point of view, licensure, the review of their documents, the approval of their documents, the

inspection of their facilities, the release of their products, and so forth, so they should pay for it.

Well, there's this fundamental rule of life which I have acquired over three-quarters of a century, which is, he who pays the piper calls the tune, and, boy, did the industry start calling the tune when PDUFA went into effect. I mean, deadlines came in, and then the deadlines got shorter and shorter and shorter and shorter, and what happened was we had some, at least in Biologics, you had some excellent people who just left and said, "I can't do what I'm really here to do," because of PDUFA.

And what was the next thing?

JS: MDUFA.

JSF: Well, there was MDUFA, but that was medical devices. But there was another one, the FDA Modernization Act, FDAMA. People said, "I'm spending a hundred percent of my time meeting PDUFA deadlines and making sure my people meet PDUFA deadlines, and then meeting the FDAMA requirements. This is not why I'm here. I'm here to protect the public. I can't do both. I'm out of here."

And so I just don't see how, as long as you have these situations in place, that you're ever going to have an FDA doing what an FDA is ostensibly here to do, which is to protect the public.

Now, there is a certain truth to the fact that any regulatory agency will in a sense end up protecting the regulated industries. I mean, after all, the first company to become licensed -- I'm using biologics terminology -- for any product has a monopoly until the

second one gets licensed. Now, sometimes that's only a day away, but sometimes it's a long time. So even forgetting about orphan drugs, which is another of my pet peeves, even forgetting about the Orphan Drug Act with seven years of exclusivity which can be built into an approval, there is this protection of the industry in that sense, that it can create a monopoly for at least some period of time.

The second thing is that the industries can always hide behind FDA and say, "Well, we meet the FDA requirements." Yes, but requirement *per se*, as the lawyers will argue, is that which is in the regulations, and the regulations take forever or a little bit longer to modify. So if you can't regulate ancillary to the regulations, you have a great deal of trouble regulating.

So there are these multiple problems which are built into the system, and so this, as I see it, is chronic and will not be escaped from, certainly, in my lifetime.

Now, can the workers do something in FDA to regulate effectively in spite of this? Well, yes. That's what they do all the time. But, in my opinion, it's very often doing it exactly like that, regulating in spite of, not because of, these laws that are in place. I'm not saying we should repeal the Public Health Service Act. It's a great Act. The idea of licensing a company is, I think, a great concept.

JS: We tried to do it in '38. It didn't work with drug companies.

JSF: And I don't think we should repeal the FD&C Act because there are a lot of good things, and there are a lot of good things in the drug regulations that, of course, Biologics relies on all the time.

But beyond that and the “other duties as assigned” that I used to do, and I did increasingly over the time after I became Associate Director for Science, Biologics increasingly had to train more and more people to do things that Biologics people had previously done. I spent a lot of time training field inspectors; I spent a lot of time training reviewers; and I tried to emphasize that, yes, it’s important to know the regulations and, at some point, know the recommendations; and it’s important to know the law when you go out on an inspection or go out to interact with the manufacturers in any way.

But that’s not enough. You’ve got to understand what it is that you’re regulating. You’ve got to understand these products. You would ideally like, when you walk onto the manufacturing floor, to know as much about that process as the director of manufacturing. And then when you walk into the lab, you’d like to know as much about those analyses as the director of quality control. And at the end of the day, the question is not simply are they adhering to the letter of the regulation, but is what they’re doing scientifically defensible, because if it doesn’t make good science, it probably doesn’t make good sense.

JS: So this is an essential tool that goes beyond the regulations, beyond the law, to understand the context of what this is all about, the science.

JSF: Right.

JS: Okay.

JSF: I think I can give you a little example on an inspection, a very small one, but I think it maybe is illustrative.

I was inspecting a manufacturer of an immune globulin for intravenous use, and one of the steps that they had there involved a batch absorption of the material; in other words, you adsorbed the product and the stuff that came through was the good stuff and what got adsorbed presumably was stuff you didn't want to have in the final product. And so when I was inspecting the warehouse, I wanted to make sure that they checked in the materials that they were going to use for the buffer that would be suspending the adsorbing agent and that would be used to wash it off. And then, when I got back around to the laboratory, I said, "Okay, let's see your QC on raw materials, let's see this same material that you're going to be using for the buffer in this step." And, of course, I checked lot numbers to make sure that they had everything they were supposed to have, that the lot numbers in the laboratory corresponded to the ones I'd seen in the warehouse, all good FDA stuff.

But I said, "Okay, how do you analyze this to qualify this raw material?"

"Oh," they said, "we've already qualified the vendor."

"Okay, that's fine. So, then what?"

"Well, then we get the certificate of analysis for each batch and we just simply do an identity test."

I said, "Okay, that's all legitimate. Show me the identity test."

"Oh, no problem." He said, "We do the USP identity test."

I said, "Fine, show it to me."

Well, he putzed around and finally opened up the right page of the USP and he said, "There."

And so, I didn't know the test myself, so I quickly read through it and I said, "Well, there's no doubt that if you have the right material there" -- see, I knew this stuff because I'd probably run at least 5,000 experiments with it myself. I said, "There's no doubt that if you have the right stuff in there, it will give you a positive color test. But anything that has a couple of hydroxyl groups and a primary amino group would also give you a positive test. Wouldn't you like to be sure that you don't just have a couple of hydroxyl groups and a primary amino group, but you really have the stuff that the label on the bottle says you have?"

He became very quiet.

Anyway, I went along about my inspection. And as I had left the Form 483 and all that and was being shown to my cab to get to my airplane to go on to the next manufacturer, the plant manager says to me, "I'd like to thank you for that suggestion. I thought you were going to bring it up in the wrap-up session, but you didn't. But I want you to know, we've already worked out an infrared spectral analysis that will detect this buffer material and will differentiate it from any of its chemical homologues, and we're going to submit this, and it will be on your desk when you get back, I guarantee it."

So that's one tiny example, I think. I tell the CBER people, you can make a difference. But in my heart of hearts, I'd say you can make a difference despite this superstructure that's trying to keep you from making a difference.

RT: I don't know whether we've covered it or not, but I thought you retired officially, I guess, from FDA in 2004.

JSF: Right.

RT: But you're still active. And would you care to say a few words about what you're doing now and how it relates to FDA?

JSF: Well, I still go into my same office. Now it's down to a couple days a week. Initially, it was simply to get cleaned up. I mean, when you work for 45 years in the very same work unit, you build up an awful lot of stuff. And at first I built it up just because of my own sort of packrat nature. But then after about maybe 15 years -- let's be more generous -- 20 years, I would get these frantic phone calls saying, "We've looked through this source and this source and this source, and we wound up in the Commissioner's office and we went to the Press Office, and nobody has a copy of this. Would you possibly have a copy of it?" and I would say, "Of course." And then, after that, I began to be afraid to throw things away.

So I built up an awful lot of stuff, and I spent the better part of at least four years simply sorting through things, and some things I just had to be absolutely brutal about and say, you know, you wish you could save these, but you can't. Memos saying who was acting head of this or that or the other thing for such a span of time; just shred them. And these are non-confidential, we can recycle those.

Then the really tough part was that other bin, if you will, of stuff. I'd say, "This should really be saved." All right. Who should have it? And then the agony would begin, first to try and decide who would be a steward of it, who would make use of it, and when would that person have a breathing spell so that I could sit down with him or her and go over it and say, "This is what the significance of this is." So, that took a long, long period of time.

Now, when I was functioning as, first as Associate Director for Science of the Division of Blood and Blood Products, and then, later, as Associate Director for Science and Acting Division Director of the Division of Hematology, and then later as, formally, Associate Director for Science for the whole Office of Blood Research and Review, for a long time I operated without a position description. And then finally, I think it was Dr. Quinnan who said, "Really, you're going to have to write one and you're going to have to get it blessed by the powers-that-be."

I said, "That's fine, no problem."

But, as I told a number of people then and since, I didn't have to have it down on paper. In fact, I didn't even have to have it in my own mind. The worker-bees figured out right away what I should be doing. They would come to me and say, "We're getting into this new area. Do you know anything about this?" "We're getting into this new area. Do you know somebody who is expert in this?" "We've done these experiments, but we're really shaky on the math, how to do the calculations right. Do you know something about this?" And, of course, the answer was almost always yes.

So, well, since I've retired, the same thing happens. People come and say, "You know, we've been doing such-and-such for a long, long time. How did we ever start

doing that?” And then you begin exploring and you find what the person’s level of sophistication is or knowledge of history is, and you fill them in. You finally bring them in and give them the documentation.

Or somebody will come with just a scientific problem. And if somebody comes to you with a scientific problem, you know what’s going to happen sooner or later. That person is going to come with a manuscript, say, “I’m going to have this officially reviewed, but would you read and review it for me before I submit it to a journal?” and, of course, the answer to that is always yes.

So I really don’t lack things to do.

RT: You’re at NIH now. Is it full time or part time over there?

JSF: Well, I go in about two days a week.

RT: What capacity are you serving there?

JSF: As I said before, I think I’m just called volunteer now, because, I mean, it’s certainly volunteer since I don’t get paid, although they do give me a hang-tag so that I can park.

JS: That’s not just a minor issue. That’s an important thing to have!

JSF: And they gave me one of these so I could get in the building.

JS: Badges are important too.

RT: Well, the point I wanted to raise or conclude on was that you're not just rocking in a rocking chair; you're still active in your field of expertise.

JSF: Yes, I try to be. Of course, when you get a manuscript that hasn't even been published yet, by definition you're at the cutting edge.

JS: That's time-consuming, though, to be reviewing manuscripts.

RT: Doctor, we certainly appreciate your giving us this interview, and we'll proceed with getting a draft to you for your review.

JS: Thank you so much, John, for coming and spending time with us.

JSF: It's been my pleasure.

END OF INTERVIEW