Oral History Interview with
Robert Frater
Cardiothoracic Surgeon
St. Jude's Medical Center

FDA Oral History Program

Final Edited Transcript

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Oral History Abstract

This interview was conducted in an effort to collect background information on the development of cardiothoracic surgery and heart valve design and surgical implantation. Dr. Frater was a pioneer in the development of heart valve replacement surgery and the technical design of heart valves, who worked at the University of Capetown Medical School, the University of Minnesota and the Mayo Clinic from the 1950s to the 1980s.

Keywords

heart valve replacement surgery; mitral valve prosthesis; cardiac surgery; medical device standards

Citation Instructions

This interview should be cited as follows:

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Interviewer Biography

Suzanne Junod, Ph.D. is an historian in the FDA History Office at the U.S. Food and Drug Administration. Soon after beginning her career at FDA in 1984, Suzanne helped to organize the FDA History Office. She is a subject matter expert in FDA history and her scholarly writings have been published in *the Food, Drug, and Cosmetic Law Journal*, the *Journal of Federal History*, and the *Journal of the History of Medicine and Allied Sciences*, as well as edited compilations. She is an active officer in the Society for History in the Federal Government. She earned her Ph.D. at Emory University in Atlanta, where she studied under James Harvey Young.

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Interview Transcript

SJ: I'm Suzanne White Junod, and we're here today with Robert Frater, a cardiothoracic surgeon. He now works for St. Jude Medical. We're at the American Association for Cardiothoracic Surgery in May 2003. Dr. Frater, can you tell us a little about your background?

RF: Well, I grew up in South Africa, where my family had been for many generations, although my mother, in fact, was born in England. She and my father had met at the Mayo Clinic, where they were both doing postgraduate work, he from South Africa, she from the U.K., and came back to South Africa, and I grew up essentially knowing I was going to be a doctor. As soon as I got past the engine-driver or locomotive-engineer stage, it was going to be medicine.

So I went to the University of Capetown Medical School, entering it, as is the case in South Africa, straight after high school at the age of eighteen. And we had in the University of Capetown at that time a quite remarkable Division of Cardiology. There was a doctor called Velva Freier, who led the division. Everybody who was an internist or a physician [unclear] for cardiologists in those days, but he had started to specialize, and he had working with him Louis Vogelpohl or Louie Vogelpohl, who had been to London to learn about phonocardiography from Paul Wood. He himself had been to America and learned about dye dilution curves at the Mayo Clinic, and we had a Robert Gertz, who had an obituary or a biography in the *Annals of Thoracic Surgery* a couple of years ago, a remarkable man who'd come out of Germany and then to Scotland, and then finally to South Africa, where he had set up a department of surgical research.

He was a person with an interest in surgery. He never really trained in it fully, but he did, for example – I'll give you the atmosphere I went to medical school in – he did triptosomography of a standard that I've never seen equaled before. I won't waste time or spend time on the very

ingenious way he did that. He had a thoracoscopic sympathectomy operation which he published in 1944 for Reynaud's phenomenon. And he had developed angiography of peripheral vessels in the mid-1940s with a rapid cassette changer he invented himself, which subsequently was more or less taken over by G.E. without any exchange of money or anything.

And so we had in the University of Capetown Medical School, when I was a student, phonocardiography, dye dilution analyses, the usual pressures and cardiac outputs, and angiography as tools for investigation. And as students, we took it for granted that was the normal. That was in fact very unusual in most parts of the world. We listened to a lecture on 100 successful cardiac catheterizations with angiography in 1949, during our physiology classes. So we all knew an immense amount of cardiology. But what were we to do with it, or what was I to do with it as somebody whose father was a surgeon and who wanted to be a surgeon himself? I could have done closed mitral, patent ductus arteriosis, co-optation, and Blalock shunt. Those were the only four operations to do.

And so I got a fellowship appointment at the Mayo Clinic.

I went first for a year to London, and young South Africans would do that in those days because we figured we had to get out of the country. We were down at the tip of Africa, isolated from the rest of the world, and we thought we had to go learn something from other places if we were ambitious at all. And so I went to the Royal College of Surgeons and did their basic science course. And while I was there, a lecture was given by Crawford, a Swedish cardiac surgeon, who described doing an atrial septal defect by dissecting the intra-atrial groove, passing a great big needle blind, with a finger guiding it, through the right atrial appendage, around the edges of an atrial [unclear] and out again, and cobbling the whole thing up to close an ASD. So I said to myself, "My golly, there's more to it than the operations." I thought, "You can get inside the

heart." And at that particular Thursday afternoon routine weekly lecture at the Royal College of Surgeons, who did I meet but Henry Suttar.

SJ: What year is this?

RF: This is 1955, 1954. I met Henry Suttar, who had done the first digital mitral commissurotomy in 1926, very [unclear]. After all, '26 to '54, that wasn't a tremendously long time after he'd done that operation, but he was philosophical about it. By now, Bailey, Harken, and Brock had started commissurotomy again, and successfully, and he had had his one great chance and had been denied it by the cardiologist.

Anyway, I then did a casualty job, and my wife and I and our newborn child went off to the Mayo Clinic, and it was pretty damned depressing because the Mayo Clinic put us into medicine. Even though I was a would-be surgeon, they said, "Well, you need to learn more medicine if you're going to be a surgeon." To my mind, this was fairly straight forward exploitation. They needed what they called, you know, they needed workers to do this and to cover the medical floors.

And I was put on a diagnostic service, and I had modest hospital duties. It was called medical urology, which meant that we saw all the patients coming to the urology service, worked them up for the surgeons, and when they came to the hospital, we worked them up to be ready for the next week's surgery. And I found myself making diagnoses in cardiology which were quite foreign to these trained general physicians in charge of this diagnostic service. They had not understood the kinds of concepts that we took for granted.

I saw a young woman with very loud pulmonary systolic click. I remember it only

because of the excitement it caused amongst the attendings, who thought, "Who's this little jerk telling us this is a case of pulmonary hypertension? It may be due to chronic pulmonary embolism from her legs. Although she has no signs of it, she's had several children. Or it may be a primary pulmonary hypertension." And they said it's pulmonary hypertension, you can feel it, and so on. And of course I was right when they got the patient ultimately. But I realized I still wanted to do cardiology, cardiac surgery more than anything.

And it was about a month after I'd gotten there – this is now September 1955 – I was getting pretty depressed being paid $1,500 a year and miles away from everywhere, 9,000 miles away from home, and I said, "I've just got to get into an operating . . ."

Saturday, I'd finished working up the prostatectomies for the next week, and I said, "I just have to get into an operating room." So on Saturday afternoon, in the old Methodist Hospital in Rochester, Minnesota, I went into the operating room, suite, and I saw a heart surgery. Oh, my God. And I went into the gallery, and the galleries were such, if that was the operating table, the gallery was that high, and you just leaned over and looked right down into the operation. You had a paper mask on and a gown which you'd picked up outside. I don't think we even had to put a cap on, if I remember correctly.

And John Curtin [could be spelled Kirklin] was the surgeon. A fellow called Harry Harshbarger, who had been a tackle for Northwestern, was the assistant. He was so damn big, I really had to lean over far to see the operation. And a fellow called Bob DeVue was giving the anesthesia. And there was this big stainless steel machine with a vertical portion down which blood was trickling on a screen. And the blood was then moved towards the patient with a roller pump put through a plastic pipe and into the patient, and coming from the patient there was another of these lines with another roller pump on it. And what they were doing, this machine

was quite extraordinary. It was an IBM-designed machine. It was a Gibbon machine which actually had a sensor – and this I only found out afterwards – on the central venous pressure and it altered the venous return by speeding up or slowing down according to the central venous pressure. And running the pump was Jeremy Swann of Swann gas fame; David Donald, a Scottish veterinarian; and a physiologist called Edwards who – not Jess Edwards the pathologist, but another Edwards who developed the G suit during the war for flyers; there was a human centrifuge in Rochester. And I realized they're operating on this kid's heart and they're using a machine to support the kid's life.

Now, I'd heard of the possibility, because while I was a student in Capetown, we actually had a lecture from a visiting Dutchman called Jon Blut, which means young blood in English, and who'd described efforts to develop a heart-lung machine that he'd been making. And of course I subsequently found out this long and interesting history of the development of heart-lung machines, but at that moment it was . . .

The next day, I said to my wife, "You know, we're going to stay longer in Rochester than we'd planned, if you don't mind, because I'm going into cardiac surgery." And she said okay.

And so I went along to the fellowship office and said, "I'd like to apply for the cardiothoracic program, which was then an add-on to the general, it was all mixed in together in terms of rotations.

Anyway, I then had to do a thesis. There were two cardiac surgeons at the Mayo Clinic at the time: John Curtin and Bucky Ellis, and Curtin was a young man. The position had been offered to Claggett, who was the senior thoracic surgeon, but he said, "I'm too old." He was in his late forties, I suppose. And he said, "Give it to John. He's just spent a year in Harvard at the Massachusetts General – or was it the Brigham – working with Gross, and he knows more about

it than I do. So he developed it.

Maybe I should say a few words about the machine.

He told me that when you wanted to go in, he did the usual thing. You go to the literature, see what's there, and he found there was a machine that Dennis had used in New York – originally from the University of Minnesota, gone to New York – and was doing cross-circulation with it, which was, by any analysis at all, was surely something you couldn't sustain, parents hooked up to children. It was just too difficult and too fraught with ethical issues and potential tragic issues and so on. And they were busy working on bubblers at the University of Minnesota, a very old form of oxygenation, goes back to the 19th century, for perfusion. And there was – Melrose in London had a machine, a disk machine, and Bjorkin had a disk for basically cerebral protection during cardiac surgery, in Sweden. He was in the Karolinska.

And Curtin came back and said the best machine is Gibbons' machine. Everybody's familiar with that, a very long story. It's kind of an anniversary this year. So they said, "Well, get it. We'll buy it," and Gibbon wouldn't sell it. Gibbon said, "Look, I've had disaster with it. I had one success and three disasters. I don't think it's – there's something wrong. I don't know what it is," and he was very determined. And Curtin kept badgering him. And eventually, on Christmas Eve, I think 1953 but possibly 1954; I think it was 1953, a Gibbons letter came saying, "All right, I will agree," and Curtin had promised him he would keep Gibbons' name attached to the machine. And Curtin went on Christmas day.

So he told me – now, I hope this is true, but it's one of these things that is clear in my memory as something that he told me – went on Christmas day to pick up the blueprints, and they made a machine at Mayo on the basis of Gibbons' blueprints. And they'd worked, Gibbon had worked with IBM in Philadelphia, and IBM had come into Rochester fairly recently,

encouraged by the opportunities so it wouldn't be a one-industry town.

And then they did ultimately, I think, ten dogs, half an hour of open heart, no procedures. I think they opened the right atrium and closed it again. And they got survivors for long enough that they decided it was good.

And so in March of 1955, they had started. I think the patient that I saw was about patient number thirty-five or so, and Curtin told me how at the end of the first year he had had 25 percent mortality. That was in 1956. And the question was, would they let him go on or not? They were fairly used to having 1 or 2 percent mortality, even in those days, from colon resections or gastrectomies and so on. And they came out and said, "You can go on," which was wonderful for him, so he continued.

And the person that I was assigned to for my thesis, since everyone had to do a master's degree as a fellow at the Mayo Clinic. I think virtually everyone did do that. And a master's degree in surgery, a master of science in surgery, a very unusual degree in the United States, very common in Britain and the British-connected places like Australia, New Zealand, India. A master's of surgery was an important degree, the equivalent of getting a Ph.D. in medicine. You had to do a thesis for it.

And I said to Dr. Ellis, you know, "What should I do?" and he said, "Well, why not develop mitral valve prosthesis." Okay.

SJ: A master's degree? [laughing]

RF: [laughing] And so I got to work. And I first, obviously, looked in the literature. There was one or two people who'd been trying to do something – I forget whose name; it's left me for

the moment – who ended up in Brooklyn – I'll think of his name – had a metal valve with a sort of a cage around it, and the idea was you put a purse string and pulled the tissues into this meshwork cage, and that would then be the attachment. So that was up, and it did not work terribly well in the few attempts at using it in dogs.

So I looked up the literature. There wasn't much. I looked up the anatomy. There wasn't much. I got specimens of deer, beaver, dog, cow, sheep, a bird, various ducks, a rat, turtle, all kinds of hearts, and I gathered them from anybody who could find me one, you know, a gamekeeper who gave me the deer, and so on. And I looked at the way the mitral valve was constructed and the way it worked, and I had some help from a fellow called Bowling. He was a physiologist at the Mayo Clinic, and Grindley, who was a marvelous man. He had been an army surgeon in Burma during the war, and he was a crusty sort of character, and he was in charge of experimental surgery. And so I had six months, by the way, for this project.

SJ: Six months?

RF: [laughing] Six months. And so I started making designs. And what Bowling and Grindley had done, which gave me a clue, which turned out to be an extraordinarily important few seconds of observation, they were making hearts beat by perfusing the heart with oxygenated Ringer's lactate, and it was clear fluid in this beating heart. The atrium was open and, of course, you looked through the water and all the liquid, the clear liquid. And I noticed the way the mitral valve was beating, and I noticed that the cordi were always under some tension, even in diastole, and I was able to get a fair idea of how the heart was working, and in particular how important the anterior leaflet was as doing most of the movement and meeting a closed valve leaflet which

was composed of approximated scallops being forced together by the pressure of the contracting annulus. And I took some movies of that.

And I then started to think of a variety of designs, and so I used silicone rubber for some, and that had four leaflets, that silicone rubber valve, and I didn't really want to make a valve that was quarterly supported because I thought it would be too difficult.

Now, working at the same time as I was, was Nina Brownwald, Dr. Brownwald's wife, and she designed a polyurethane valve, mitral valve, made out of polyurethane foam in which was incorporated a series of polyester chordal that came to two sort of thick polyester sutures and were then pushed through the ventricle to be tightened up outside.

At any rate, we ended up with a mono leaflet valve which had flexion across multiple hinges and stiffness parallel to those hinges in some bars of Mylar was the substance we used. And we had used, we went out to Dow Corning, looking at various adhesives, and really that was with Crazy Glue, actually, which we joined the stuff together with, and then made multiple laminates to make the ring and then put on the outside of the ring a porous sewing ring.

Now, we got to the porous sewing ring by implanting partially compressed ivalon sponge donuts above the tricuspid orifice under inflow stasis, and we showed that in three months that porous ivalon ring – if you compress it too much, of course, it became solid, so you couldn't. It would have no invasion – had been invaded by fibrous tissue and covered by it as the sort of pseudo-intima. That gave us the clue to the proper design of the sewing ring. You had to have a porous sewing ring, one which the tissues could invade and replace the sutures.

So we made our sewing ring out of an ivalon sponge attached to the outside of the more stiff portion of the [unclear], which was de-shaped to imitate nature, and the large and only leaflet that opened out of the way of the blood and closed back against the ring had its straight

side on the straight side of the ring, and that was the part that was put under the aorta. So this valve opened around the way a turtle heart opens, which is only one leaflet, or the way a mitral valve does most of the moving.

And we did dog work, and our longest dog survived for some eighty-five days. We did no real wear testing. We didn't quite know how to make an accelerated wear tester. The valve that was in there for eighty-five days looked fine when it came out. We found that there was an enormous tendency for embolism to form. We found that clots would form on the valve extremely quickly, build up out to the orifice, and at the orifice would, depending on the flow, start expanding into the flow and growing into the flow, and then break off and cause an embolism, or cross and meet and thrombose the valve. But we found that these, this particular design could be helped by placing the residual leaflet tissue over the ring, so putting it essentially subannular. And with that kind of insertion, we found that these dogs seemed to be surviving without emboli.

Interestingly enough, if we put it the other way around so that it opened towards the septum and there was in fact a dead space behind the open leaflet against the mirror annulus in diastole, the thrombus would form behind there. Obviously, there was an area of stasis from a slow-moving vortex that formed behind there.

And, by the way, we did test this valve in a pulse duplicator, and we had atrial ventricular pressures and we had blue dye injected into the ventricle so we could see what insufficiency there was and could also see, as the fluid flowed through it, what the flow pattern was like. And we took cinnies of this.

SJ: You took what?

RF: Cinny pictures, 16mm cinematography.

SJ: I think that's a British word. Okay.

RF: Cinnies? It's a medical term. We use it very frequently. Cinematography is where it comes from.

SJ: Well, that is definitely important.

RF: And Dr. Ellis said, "I think we're ready to do patients." So I made some adult-sized valves up and I sewed them, sewed the ring . . .

SJ: And what year is this?

RF: This is 1960 now. My thesis started in 1959, ended in January 1960, and so now it's June 1960.

SJ: And you've got the degree, right?

RF: My thesis hasn't been awarded yet.

SJ: So you took longer than six months.

RF: Six months was the period in the lab.

SJ: The research.

RF: I'm back on the service now for the last six months.

SJ: Okay, got it.

RF: So I made up these adult valves, so, and we decided to cover them with knitted Dacron cloth. The principle we had worked out was that we're going to get protein deposition, starting with fibrin for sure, certainly albumin – we knew that – within hours of putting this device in the circulation. So long as the flow pattern was unlucky to allow for stasis, and so long as there was a surface to which thrombus would cling, we figured that we were going to be safe from the development of embolism.

And so we had a valve, which was a flexible, called a flexible mono cusp covered in a very thin layer, a single layer of light knitted Dacron, and it was Dacron over the ivalon sewing ring, and we did two patients, I think on June the 7th and June the 16th, 1960. One patient was a Capital Airlines pilot.

Capital Airlines is long since defunct. We had traveled, in fact, on Capital Airlines from Rochester to Dow Corning, had been in Michigan when we went to the Corning people to see what materials they might help us with. And I knew that airline was going broke because the airline hostesses were in carpet surplus. [laughter] Well, I said to my companion, "There's

something funny about this airline." Never saw airline hostesses in carpet reminants before. Their morale must be low.

Anyway, he was a Capital Airlines pilot who had been flying with heart failure, just to give you an idea. The FAA wasn't as shocked as it is today. And he had actually had an attempt at an annular prosthesis, and it had failed, so they decided he needed a valve replacement. It was about six months after his annular prosthesis. And he left the hospital nine days after surgery with an excellent heart sound. You really couldn't tell the difference. His primary aortic pressure had been very high. I still have the pressure record of the fall in left atrial pressure, which we measured. And we did, of course, cardiac outputs with dye dilution and so on.

The second patient was a female, younger, and similarly sick person, and low cardiac index, severe pulmonary hypertension, dominant mitral insufficiency, birth rheumatics probably originally, and she came through fine, too, nine days after surgery. I'm sorry, it wasn't a female. I'm thinking of the third patient. It was a male, it was a male.

So these two patients left the hospital alive, and there had been no IRB nor, certainly, any regulatory approval from FDA or any other body. There had been an agreement amongst the staff, John Curtin and Bunky and, no doubt, the cardiologists that these patients had no future without surgery, without an attempt to correct their mitral insufficiency. We know what the prognosis is. They've already been in heart failure and they've got a limited life.

We had conscientiously tried to find out what we could about the ideas we had. Had we been more cautious, perhaps more willing or more desirous of being absolutely certain, we, of course, would not have started. We had to start with uncertainty.

I think, you know, I mean, one thinks about those kinds of things. I made those two valves.

SJ: What options did they have at this point?

RF: They had the option of digitalis and mercury, mercury diuretics, digitalis. There was no lidocaine, there was no modern type of diuretic, and digitalis was the drug of choice. There was adrenalin to be used in the operating room, and there was even – what was the other one? – another form of adrenalin, which I'll think of in a second, not noradrenalin, another one. But, at any rate, those were the agents that we had.

So, people with rheumatic fever died. They quite often didn't die until they were in their thirties, but generally about thirty years after making the diagnosis was about the time they died, after it had been picked up in childhood. We didn't really know about myopathic heart failure then. We figured it was all due to the valve. And there were other diagnoses, which you might recover, but, you know, you might recover from endocarditis if you had a valve lesion, but you were going to die if that lesion was resulting in either a blocked or a leaking valve.

So they didn't have any other options, and so we had to be prepared that we would, that we might fail. We had to be prepared that the device might fail. And we did, in fact, tell the patients that we don't know what's going to happen. It's all we've got. If you want to try it, we're willing to try it with you.

Can we stop?

SJ: Yes.

[END OF TAPE 1, SIDE A]

RF: Three months, or just under three months after the first operation, we got a call on a Friday night, actually, late on Friday night, that our first patient had been watching the Friday night high school football game in Marshall Town, Iowa, and had died on the stand in front of the hotel, and they were going to do an autopsy on him in the morning and they wanted us to know. So we hired a plane, a Beechcraft. We flew down from Rochester to Marshall Town, which wasn't very far. We landed on a flying field which had corn growing on it. I remember it very well because there was a small runway, grass runway, and the corn was higher than the wings when I looked out as we landed.

And we went to the funeral parlor where there were a whole lot of town people – they couldn't all have been relatives – packed into the funeral parlor to watch the autopsy. And we opened up the atrium, and the suture which had been used to put the valve in was 3-0 running silk. Why had we used 3-0 running silk? Because that's what had worked extremely well in the normal dogs. But in this rheumatic patient with a rather scarred annular area, healing into our sewing ring had not taken place, so – by the dog, that would be absolutely socked in in three months of time – and the suture had broken. 3-0 silk is incredibly weak by comparison to what we use today. And so he died of an acute disruption of the valve. The valve was intact. And so that was the first patient.

In September, I think the 9th and 10th of 1960, there was the first meeting on artificial heart valves. It was called Artificial Valves for Cardiac Surgery. Merindino had pulled it together, and the NIH had financed it. It was held in Chicago. I used to think it was the Palmer House, but I think it was not the Palmer House. I'll have to try and look it up to see what hotel it was in. And on Friday evening . . .

SJ: Do you still have the program?

RF: Yes. I don't have the program. I have the book that was published from it.

On Friday evening, there was a cocktail party, as there usually is, a reception, and Hufnagel came up to me and said, "I thought you'd be interested in these photographs. I took them yesterday." And they were color photographs, and I don't know, they must have been colored Polaroids, I think, but there wasn't color Polaroid photography at that time. I don't know how he got a color photograph in less than twenty-four hours. I still have the color photograph. And there's his thumb in it, and he's holding the atrium open, and it was the same picture as the one we had seen in the autopsy.

We had gone to that conference as the only people in the world with a live patient who had had a mitral valve replacement. And, of course, by the time we got to the conference, there was no patient in the world alive with mitral valve prosthesis. Nina Brownwald had done the first. Ours were the second and third to leave the hospital. We don't know others who might have been done elsewhere that didn't leave hospitals. Nina's patient, put in by Glenn Morrown, built by her, had left the hospital. It had been several patients before then before they finally had a success. But the success, she left, that patient left and died about three to four months later for reasons they couldn't determine. I don't know whether they got an autopsy or not, but they couldn't determine.

Our staff had tried, about ten days before the conference, so that he, you know, he obviously wanted to have a live patient for the conference, and that patient died of air embolism, a massive air embolism, and that was obviously part of the learning curve of how to do mitral

valve surgery.

So there was no live patient.

SJ: But wait a minute. Your first patient died. Your second one had died at that point?

RF: That's – Hufnagel showed us the . . .

SJ: Oh, I'm sorry. Okay. I didn't catch that.

RF: Hufnagel showed us the picture.

SJ: And he had died the same way basically that the first one did.

RF: Yeah. And that valve continued to be put in by Ellis. It was made . . . I left in '60, having completed my fellowship. Sorry, I left in '61. And the valve was made by the people at IBM, and there were a series of them done and compared with the Starr ball valve, which they also started using fairly soon after then, and they published this. The incidence of thrombo-embolism was very much less. Of course, there was not anticoagulating the patients. But ours did not have any significant emboli, whereas the Starr valve had a whole lot and they realized they were going to have to give it, give the patients anticoagulants.

But what happened basically was that ours was an amateur effort, and even when the IBM people were making it, it was sort of a favor and it wasn't done for money or anything.

The great difference with Al Starr's valve was that he had Edwards, the engineer, with

him, and everything, from the beginning, was done by an engineer, not by amateurs. And, as a result, that valve became a success. I should add that the longest dog survivor that Al Starr had before he put his first valve into a patient was seventeen days, and he had announced that the dog is too difficult an animal to do valve replacement surgery, and we have to go straight to humans. Our approach had been different at the clinic, and we got up to eighty-eight days, or eighty-five. I can't remember. I'll have to look that number up. And so Al's valve was then a success.

I went on to work on pericardium or autogenous pericardium for constructing valve repairs, feeling that we could get a very long way with repairs rather than replace, and I had a whole series of chordal replacements, leaflet extensions, transfer of cordi from the [unclear] to the [unclear] when they [unclear] cordi, so we'd shorten them by taking the posterior leaf of the [unclear] and filling in the rest with the guts of the pericardium. That, too, failed in time because of the body's response to autogenous pericardium.

Now, what was happening in the next five years or so was that many valve designs began to come along. The testing was dependent on the conscientiousness of the people doing it, and most of them were very conscientious, trying very hard, as we had been. I feel quite good about what we were trying to do then. We were working with an enormous level of ignorance. If you analyze what we did in the early cardiac open-heart cases, we did not have blood gases; we did not have radial artery pressure or any other form of pressure except a blood-pressure cuff and a finger; we did not have electrolytes; we did not have an EKG monitor. We took two paper EKG's a day to see what the patient's rhythm was, and in the operating room, we looked at the heart and analyzed it with our eyes as to whether the atrium and ventricle were in synchrony and so on. And we would weigh our patients – they were mostly children because they had congenital heart disease – by standing on a scale with a baby in our hands, and then knowing the

weight of the dressings and the tubes and so on, and we would control our fluid balance by weighing the patients and watching the urine output and watching their weight. And despite that, we actually got 100 VSD's in succession without a mortality in 1961 with John Curtin.

I went back to South Africa and started working with Chris Barnard, who had been for two years to the University of Minnesota, the [unclear], and in those two years got both a master's degree and a Ph.D. degree in surgery, which is pretty darn good, and he had come back as the one-eyed man in the kingdom of the blind to Capetown.

We'd had a wartime thoracic surgeon, first-class pulmonary surgeon, done good work in trauma surgery in the war, learned how to do closed mitral commissurotomies pretty well from Brock, and thought he could do open-heart surgery by just coming on a quick trip to the United States and buying a pump, and it hadn't worked. Barnard made it work in Capetown even though he was not even qualified to be a surgeon. He hadn't done enough surgery to qualify as a surgeon. But, as I said, in that atmosphere and with this fantastic department of cardiology, they brought him through. I don't want to divert too far from the subject at hand, which is the FDA, so I don't really. . .

SJ: Keep going. We've got plenty of time. Keep going.

RF: Okay.

SJ: We can finish later if we don't finish now.

RF: The way Dr. Schirra brought Dr. Barnard on in cardiac surgery was to line up for him

twenty atrial septal defects; twenty pulmonary stenoses, the two simplest open-heart operations that you could do; twenty VSD's – now we're reaching a higher level of complexity; and then, finally, his first tetralogy of Fallot, which has a combination of ventricular septal defect and pulmonary stenosis. And it was such a sort of extraordinarily smart thing to do for a cardiologist not to do the conventional thing, which is give the most difficult case in a new area, a case that's going to die anyhow, but to give him the simplest case and have the faith in his abilities and his ability to organize a heart-lung team, and we really were a team from the beginning in Capetown, absolutely. We never had any sort of individualism, except Barnard's individualism, interfering with the working of the team.

And Barnard then got hepatitis, and he was sick. Hepatitis has been a hazard for cardiac surgeons ever since the very beginning. Don't forget, we used to draw fifteen units of fresh, warm blood to do our cases at the Mayo Clinic at six o'clock in the morning, before surgery.

Anyway, Barnard announced that there would be no more cardiac surgery until I recover, and Schirra went to see him and said, "What do you mean there'll be no more cardiac surgery? I want to have cardiac surgery in the University of Capetown, and we invited Frater to come back from the Mayo Clinic," where you got *the* best education he could have in those days outside of the University of Minnesota. The two best places were undoubtedly in Minnesota, the clinic and the university. "And he's going to continue doing cardiac surgery because I want to have two cardiac surgeons here. I don't want my program to stop every time some surgeon is sick." And he said, "You're too sick to argue with me." And Barnard couldn't argue with him.

And I heard this, the fact that the cardiac thing was going to continue, and I ran down to Ward C3, and I saw a fellow and he had this enormous heart swelling, sort of red and angry coming through his chest. It was an aneurysm, encephalitic ascending aortic aneurysm that was

eroding through the sternum and was under the skin, you see. And I ran to Paul. I said, "Paul, I'm going to operate tomorrow. There's a fantastic patient in C3." He says, "I know that patient."

I said, "Well, I'm going to do him tomorrow."

He says, "You're not."

I said, "What do you mean, I'm not going to do him? He's got to be done."

"No, he's not going to be done."

"He's going to die if I don't operate on him!"

He says, "He's going to die if you do operate on him."

I've put an ASD on the schedule for tomorrow, and you're going to do that ASD."

Now that, to me, was such an extraordinary act. If I think of the way cardiologists have behaved in other areas with cardiac surgeons, he saved my life. I would have operated on this chap, there would have been blood on the ceiling, the patient would have died on the table, and they would have said, "Look, Barnard had a series of successes, and this guy Frater comes back from America and thinks he's full of it, he thinks he's just the cat's pajamas, and he kills his first patient," because Barnard had promised me a case a week, but then it had never come, and I kept on asking, "When am I going to get my case?" "Don't worry, you're going to get a case, you're going to get a case." It never happened. And so I was so keen to go.

Anyway, we then decided that we needed to develop heart valves too. Now, my heart valve was essentially dead because I'd left the clinic, and the clinic had been using it, but it wasn't being made by anybody.

We had an extraordinary Jack-of-all-trades in our department, a fellow called Gursen or Hursen as you'd say in Afrikaans, who could run a heart-lung machine, who could take

photographs, who could fix up anything electrical, who could work a lathe, and we started working on another heart valve. And we in fact made a mitral valve and an aortic valve, with silicone poppets to close them, stainless steel, machined out of a single block of stainless steel, with a ring and the holders. Those parts that were strained or somehow contained the poppets of the aortic valve looked like an Apollo space capsule with two sort of poles on the end of it, and it moved up and down with two rings around those poles, so that it had round on the bottom to meet the ring and curved off at the top. And its flow pattern, as judged by tea leaves floating in a pulse duplicator, was absolutely smooth. The flow just came around in the smoothest convention. And we used that valve without any coagulation, and we actually did not get emboli with that valve. There was no area of stasis in relation to that valve at all, and there was great washing of the junction of tissue and inorganic material with every beat.

The mitral valve was not so successful. It was a funny sort of disk on a pole with a T on the top of the pole, and that also moved up and down in a ring extension from the sewing ring. But those valves were made in our department by the perfusionist, barely tested in animals. This was Barnard's. As far as animal testing that I had done on my valve at the clinic, tested in a pulse duplicator to show that they opened and closed appropriately, not really tested in a wear test because, again, wear testing had not yet come along.

And the valve was a great success, worked for a long, long time, and only really stopped when Gursen finally got tired of all the abuse he had from Chris as a routine. He always got abuse from Chris because Chris, that's the way he behaved in the operating room.

And once Gursen left and went to America, where he emigrated, he did extraordinarily well and is now retired, living in Florida. Of course, it stopped being made.

So then it became necessary as time went on that you had to, you could no longer make

your own valves, you had to get a company to make them. And Barnard then started using Starr ball valves or whatever was coming on the market. And there were many more valves coming on the market all the time at that time.

There are now books which you can look at which chronicle hundreds – you've got some of them? – chronicle the many different designs.

Clark, Dick Clark, who was I think in St. Louis at the time and ended up at the NIH, started – and he had been an engineer – started the notion of accelerated wear testing, and another fellow called Swanson was involved, and the two of them, not necessarily working together but certainly collaborating sometimes, developed the notion that you could do wear testing by speeding up the rate of opening and closing in the machine, and he began to develop some principles of it.

And, you know, the pig valve, of course, came out of, originally from Europe, the tanned pig valve, first Oxford with Gunning and Duran, and then Carpentier and Jean-Paul Binet developed – Binet developed a formaldehyde-treated pig valve. Alfgaining and Carlor developed a stent, and they were using it initially to put fascialata on it and around it to make a pretty good valve with this rather good fibrous tissue from the thigh. I had kind of given up on pericardium because autogenous pericardium, untreated, invariably scarred up. And so there were these various people working in various directions.

The homograft had come in quite early, but that was so difficult to procure in many parts of the world, and probably certainly more difficult to use. Donald Ross used it, but [unclear], somewhat independently of Donald, started using it. Jim Malm in New York started using it. John Curtin to some extent, but it was very small use. And, of course, no regulation on that at all. Again, your conscience and what constitutes sterility and how can you prove sterility.

Where the aldehyde tanned pig valve came along, it had in fact virtually no control at that time from any device agency. And Hancock and others would just sort of declare what its properties were, but producing very little evidence to demonstrate it.

We had done a lot more work – when I say we, I mean I and colleagues in my lab – trying to do good hemodynamic, fluid dynamic testing. And when the Ionescu-Shiley valve came along, here is now a manufactured valve as opposed to a harvested valve, and because it was manufactured and the pericardium was mounted around the outside of the valve, it was possible to get better hemodynamics than the pig valves had shown. So it was largely on hemodynamic grounds, not on durability grounds or other performance grounds, that the Ionescu valve began to be popular.

And we then embarked on our own studies with a fluid dynamics engineer to try and decide what constituted proper testing in fluid dynamics. I mean, there are principles which up to this day – in fact, there's a paper in this meeting talking about the correct way to describe the performance of a valve is to relate the effective orifice area to the mounting size or to annular size, they call it. We called that the performance index, and we published papers, and we published papers on that in the '60s.

At the second valve conference in 1968, which was held at the Century Plaza Hotel in Los Angeles, run by a fellow from the Mormon university, Seventh Day Adventist University – what was his name, a tall fellow? I'll think of it in just a moment.

And so there were individual labs, Dick Clark's lab and Swanson's lab, trying to do wear testing; our lab describing the proper principles for categorizing and describing the flow through and the regurgitation backwards through a valve, and I'm sure other people were doing it too, but we certainly were prominent at that time. And the reason why we were able to do it was because

we had a fluid dynamics engineer who'd come to work with us, an interesting fellow. He'd lost his job because of McCarthy, because he had been a communist. He lost his job in Seattle, and he came, and we gave him a job, and it was a wonderful, wonderful time we had together, [unclear] Yellin.

And then we started using, we were the first in the country to use the Ionescu-Shiley valve because we had tested it hemodynamically against the other available devices and said it was better hemodynamically. We were pretty unsophisticated because we didn't really recognize that you didn't have to have a perfect valve to benefit the patient, but it was better. And we published some data, some early data, on its better performance.

Now we're talking about the '70s, the mid-'70s.

SJ: Tell me a little bit – and you may be getting to this in the '70s; I just remember when we had our original conversation, you had some wonderful stories about the crazy marketplace and how some of the valves came and went without as much rhyme and reason as you might think.

RF: Well, there was always the question of, if somebody was making a valve, they had to be selling it to be able to continue making it. The money for those ventures, I don't really know how it was raised, frankly. I don't know how much venture capital was in it, I think relatively little. I think it was more like loans and/or somebody's independent wealth that enabled them to start doing something. Or it was a company that had other products that were successfully being sold, and they tried to venture into this glamorous new field.

And certainly Shiley was – Shiley was an engineer who figured he knew how to make valves, mechanical valves. Edwards was an engineer who figured he knew how to make

mechanical valves. Both were acquired by big companies after they'd had some success as small, starter companies. Pfizer bought Shiley and Baxter bought Edwards. Actually, American Hospitals bought Edwards first, and then Baxter.

I'm not sure what I was talking about then. It doesn't immediately come to me what particular things I was saying. But let me go on a little bit.

We had our first incident with an Ionescu valve in a patient who was one year post-op with a mitral valve in place. He was admitted to the emergency room with some chest pain, and a relatively – we were very early into echo, and the echo showed evidence . . . No, wait a minute. It was not echo. It was an angiogram. Sorry, I'm wrong. That case was not an echo. He had developed a systolic murmur, so we took, we did an angiogram, a ventriculogram, and a jet of insufficiency came out adjacent to the annulus, and we thought it was perivalvular. And two months later, the patient came in in pulmonary edema and died, and in autopsy there was a tear from post all the way around to the belly of the leaflet along the edge of the rigid Ionescu-Shiley stent, along with the strut, which was cloth-covered, and we looked at it and we wondered why it had been a jet of insufficiency at the base of the valve to start with, and we reasoned that a tear might have occurred there and worked its way back up to the top and broken away.

Now, there was always a stitch across the leaflets at the top of each post, and it was tempting to say, well, that stitch must have started it, but we knew this had come as a jet from the base of the valve to start with.

So we decided we needed to do wear testing, and we set up in very quick order a wear-testing system which we'd built ourselves. We had some guys skilled at instrumentation, as in Capetown, we had Gursen; in New York, we had a couple of guys down in the basement who could turn something out for us, and we built a wear tester. And we knew that we had to try and

see that it opened and closed with each beat, and we used a strobe for that. And we didn't really know how we could measure the pressures at such high frequency, and we did eventually learn how to do it. But we started on testing of a series of Ionescu valves, and we found, as we watched them in the machines, going at 1,800 cycles a minute, which is far faster than anybody tests a valve now, that tears would develop commonly along the belly of the leaflet close to where, right at its contact with this fabric that tore, occasionally up at the top, but it would then, from a small tear, would spread. And we reasoned by observation that when you saw there was contact with the cloth, and we reasoned that this was an abrasion wear problem. And we published a paper on that.

And, as a result of it, of course, we stopped using the valve. And here's where the need for control came in. Because we told Marian what was happening, the Romanian surgeon in Leeds who invented the valve, Marian wasn't 100 percent straightforward with us. He said he'd never seen it, and maybe he hadn't. And we approached Shiley about it, and they said we didn't know how to put a valve in. And we stopped using it and were pretty damned sure we had established the cause. And as we went on following our patients, we found other patients developing the complication – almost all mitrals, almost all big mitrals, where the relationship between sickness of pericardium and size of the valve and stress on the closed leaflets was highly likely to be acting rather more easily in the big valves than in the small valves. We also figured, we learned something about procurement . . .

[END OF TAPE 1, SIDE B]

RF: We learned that pericardium was being harvested from a variety of slaughterhouses

around the country, put into saline, and trucked across the country, and that it could be forty-eight hours at relatively high ambient temperatures that the pericardium had been in transport. We recognized that there was great variability in the time at which tears would occur, and we reasoned that it was possibly because of irregular procurement or insufficient quality control of the pericardium while in transport and at the factory, and perhaps, perhaps variations in autodigestion and bacterial contamination of that pericardium before it got sterilized.

And then, finally, we also thought that since this was a handmade device, and you can make, a bad tailor can make a pair of trousers that tears as soon as you bend over or shift your shoulder or something, that some of the sewers may have had more contact in the valves they produced with the leaflet material and the club of the ring than others, because there was clearly a difference. And so we published some material on this.

And we then were offered, because we had become people who'd used the Ionescu-Shiley, offered the use of a series of other new valves made out of pericardium. Hancock made a valve, Ionescu came out with the Ionescu 2, and in meetings with Marian, he told me how he'd been trying very hard to make the Shiley Company put a pericardial covering rather than a cloth covering on the frame of the stent. And, indeed, they had in-house data which showed that pericardium-covered stents did not have the breakage rate.

When I asked them what they had done in terms of testing beforehand, they of course said we hadn't tested it, because there was no way to test it beforehand, before it came on the market. Our testing was one of the very first papers to make a systematic effort to define something like this.

SJ: And what year was that published, roughly? We can check.

RF: Seventy something, ’72, something like that. I could get you my bibliography, my CV from my secretary. It’s got those things all buried in there somewhere.

And Marian told me of his great frustration because Bruce Fitell, the CEO of Shiley, was not interested in making a change until they’d gone through the whole process of now they were beginning to develop a testing program. He didn’t want to do it, and there was reluctance on Bruce’s part, and I think the reluctance was related to admitting there was something wrong with the valve, which he never did admit, and taking care of inventory, you know, that sort of thing. So, that may be an unfair characterization, but it’s the impression I got, and Marian was frustrated, there was no argument about it.

And then we tested in our wear tester. At this time, the late ‘70s by now, when new valves are coming into use and under test; maybe it was by the mid-‘70s before we . . . No, it must have been the late ‘70s, sorry, that we did our testing, not ’72, late ‘70s. And now it was early ‘80s, about 1980 or so, where we were testing a new valve produced by Edwards. The Hancock 2, the Ionescu 2, and the Mitroflow.

The Hancock 2 was horrible in terms of its wear testing, fantastic with hemodynamics, the best hemodynamics and the worst wear testing.

The Ionescu 2 was only marginally better hemodynamically, if at all, than the earlier Ionescu, and very poor in wear testing.

The Edwards was reasonably good on wear testing and fair on hemodynamics, not as good as the Hancock 2, but it was certainly better than the Ionescu and certainly better than the concurrent pig valve would have been, or was, as we tested them.

And the Mitroflow was not too far off the Edwards in durability.

And, mind you, all of these were not lasting 100 million cycles. They were failing much before then. And I think our system was excessively destructive at the rate we were running, and we really began to learn how to do pressures. We were able to get instantaneous, brief, the spikes of pressure, and we knew what the spike, very short-lived spike of systolic pressure was in these valves.

SJ: From patients.

RF: No, from the machines, from our machines, you see. We were developing . . .

SJ: The machines could measure that.

RF: There was no guidance to tell us what we should do.

And, anyway, we chose to use the Edwards, and not in the mitral position. We chose to use it only in the aortic position and told Edwards so. And so we were then in the trial, the FDA trial of the Edwards valve, from ’82 to ’84.

And, at the same time – I’m trying to remember.

Anyway, from our point of view, we had developed a way of looking at valves, and AMI at that time started – and I was on the valve standards committee, the valve committee – and we started to develop a sort of a template for testing valves *in vitro* and began to approach the animal testing, where we really never knew what good animal testing would be. The dog was clearly not a very good model. We hadn’t come upon the sheep yet because the one who did that was Jones at the NIH.

SJ: Why was the dog not a good model?

RF: It gets bacterial endocarditis extremely easily. It gets bacteremia far more commonly than other animals do. I guess carnivores may get bacteremia more easily, I don't know, than ruminants, but it was extremely prone to endocarditis. Quite a good model to operate on, quite nice anatomy, but not at all good to look after long term.

I'm trying to think of when the Pfizer, the Bjork-Shiley thing, began to blow up, sometime in the late '70s, I believe, and early '80s.

SJ: Perhaps '75 to '83-ish.

RF: The point being that Bruce Fitell behaved in exactly the same way with the Shiley as – with the Bjork-Shiley as he behaved with the Ionescu-Shiley. A couple of . . .

You know, the valve had been working well. It had thrombosed from time to time with poor anticoagulation and would thrombose in the lesser orifice, and the Shiley people recognized this and therefore changed the design with a circle CC, concave and convex, to make it – they shifted the axis close to the center, and so the secondary orifice became bigger. And it became very quickly apparent that the incidence of thrombosis had clearly dropped – not the incidence of embolism, which is a different phenomenon from thrombosis. Embolism comes from the interface at the edge of the valve between tissue that's grown there and inorganic material. If there's any kind of stasis area, then these little different aggregates build up and break away. But thrombosis of the valve is related to a sort of red clot forming in an area of stasis relative to the

valve, and that was much better with the new Bjork-Shiley.

And then the strut, the output strut fractures began to occur, and it was very evident that Bruce knew about them, Bjork surely knew about them. Bjork was trying very hard – and I'm sure you're familiar with the famous letters that were written – trying very hard to get them to change. And I spoke to Bruce, and the FDA – this was my first knowledge of an FDA group beginning to interact, not with a guidance, not with an attempt to set standards, but with complaints that came to their ears and which made them say, "There must be something. Can you tell us about it?" And Bruce Fitell's response was, "They're a bunch of jerks that don't know what they're talking about, and I don't have to listen to them at all."

And it wasn't the FDA that closed Bruce down. I think I can probably fairly say that. It was the fact that it became so much public knowledge that this valve. was failing, and there was such an outcry from the people following patients and trying to analyze them. And tell me if I'm wrong, please, that the company realized they had to stop, and Bruce realized that he had to, he could not possibly resist the FDA's efforts to get information anymore, and the company realized that they had such a hot potato in their hands that they just quit. They kept on with the new design, which was already well advanced by then and which Bruce did not want to introduce till it was ready to go because he wanted to have uninterrupted sales. And I think I can say that with fair accuracy. I don't believe that's an incorrect statement. And anyway, he brought Shiley down. The company ceased to function after that.

Pfizer recognized they had a bunch of losses on their hands, and the litigation lawyers were just beginning to understand the concept of a class-action suit and what they could do with a class-action suit. And Pfizer stopped because it was a terrible investment and it was going to lose them money if they didn't stop.

But I believe it was Bruce Fitell's intransigence, his arrogance, and his behavior towards the FDA that made the FDA recognize that they had to start making a law about this. And '86 was the year in which they first . . .

SJ: Seventy-six.

RF: Sorry, '76, right. Not '86, of course not. Seventy-six was the time when they brought that in.

So Shiley had had sort of two valves fail in fairly short order, one of which, neither of which could necessarily have been anticipated, although if the Bjork-Shiley people had done proper wear testing, which they did not do when the first strut failures occurred, and subsequently, of course, they did an immensely, a rather good piece of work that essentially worked for Shiley, who'd been a fluid dynamics engineer himself, and worked for Shiley in the sort of, during the bankruptcy period and during the litigation period, getting to the bottom of the cause.

SJ: Did you ever do any wear testing of the Bjork-Shiley?

RF: No, no. I never did any.

SJ: Didn't use it.

RF: I just knew. I didn't use – I used the Shiley once or twice maybe. But I never was a

regular user of it.

After I stopped using the Capetown valves, I did briefly use a valve – what was his name? – a valve which is a Teflon, a caged disk valve, Teflon-covered cage and a Teflon disk. What was his name from Texas?

FJ: Beall, Bell?

RF: Beall, Beall, the Beall valve, which indeed wore out, and that was a relatively brief period. I never used a Starr valve. I think I put one Starr valve in in my life, probably because I frankly thought it was hemodynamically not all that good and, in the mitral position, tended to poke across and hit the septum if it was anything but a much dilated ventricle and give ventricular arrhythmias.

And then I used the, started to use the St. Jude valve until St. Jude was sued by Carver Medics for trying to make their own pirated carbon, at which point I went to use the Medtronic Hall valve, and I used the Medtronic Hall valve for a good number of years, until it became apparent that there were hazards in the use of it in terms of suture entrapment, and at that point St. Jude was back on track, so I went to the St. Jude valve after that for a mechanical valve.

FJ: Was the trouble with the Hall Medtronic in terms of insertion?

RF: If you have – a suture can catch on the hooks in a mitral insertion very easily. A suture can catch, and they can catch but you can't see them. The hook is deep. A suture can catch on the invisible hook of the, in the aortic position during the closure of the aortotomy. I saw that

happen once. I saw the opposite happen. And I saw a most weird one once where a suture had been caught around the hook that was invisible in the mitral position in line with the axis of the valve, so when you tilted the valve to look behind it, you couldn't see the suture, but which, at one point, had contact with the disk every time the valve closed. And a month after surgery, it broke, and that long piece of suture came away, of course, from the hook and got into the orifice, and as soon as it got into the orifice, the valve jammed tight shut.

And it was one of my patients, and I'd gone down – it was a coroner's autopsy. Some kid died at home. It was a young woman; she'd died at home. And I went down to the coroner and insisted that he examine the heart, because otherwise he'd never know why this patient had died, and we found this valve jammed by a suture.

And you know what the sad thing about that was? I was going to publish it, but the lawyers, the defense lawyers for the hospital, refused to let me publish it. And, of course, they . . . The case was ultimately thrown out, I think, and it's still sitting there waiting to be published. It's one of those half-written manuscripts that never sees the light of day. You must have seen them. [laughs]

FJ: Oh, yes. You've given us quite a bit, and it is getting close to six o'clock, so I want to honor your time as well.

RF: Fine, thank you.

Male: And you wanted to go over to your hotel before you went back.

RF: Wonderful. I think I really would like to. Look, I'll be happy to meet you anytime, you know. Clearly . . .

SJ: This is a good thing to get started on in understanding the history of heart valves and their regulation.

RF: My most important relationship with standards was related to AMI, you see, and the fact that we were trying to develop standards before the FDA, I think, had really developed standards of their own. And then ultimately, of course, there was cooperation years later between [unclear] and other European agencies and FDA to try to get to some harmonized standard, and I think with a bit of luck, that'll happen.

But it's still, unfortunately, a very difficult area because the testing methods are still uncertain. And you know, for example, the Copper Medics oxidation-treated pericardial valve, which tested beautifully in the tester, wear tester, but subsequently realized was probably not moving through a full cycle because it was so much more, or through a cycle that allowed the potential for abrasion wear to occur, because it was so pliable, it sort of floated out of the way, and then that valve, fifteen years after the Ionescu valve had had abrasion-wear test, developed abrasion wear. You'd think by now, my God, we should never design another pericardial valve that could have abrasion wear, but it happened.

It's a very interesting subject. We've gone from primitive absence of any form of proper testing to serious efforts at doing a job of testing, but largely individual efforts without agreement on what should be a standard.

And with the fluid dynamics, it's very interesting. The FDA at one point had a series of

standard valves that they passed around to ten or eleven different labs to do fluid-dynamic testing *in vitro*, and that you should be able to get to. It's sort of an art, but it is reproducible. Every single lab had a different answer.

SJ: That's interesting and I will study . . .

RF: And that was an effort by FDA to get some science into this thing.

SJ: Well, thank you so much.

[END OF INTERVIEW]