Dr. Steven Phillips: Dr. Frazier, we are just honored to have you here at the NIH and National Library of Medicine on this beautiful July day. As you know, this interview is part of the Project Bionics program, which is a partnership between the American Society for Artificial Internal Organs, ASAIO, the Smithsonian Institution and the History of Medicine Division for the National Library of Medicine. We have been doing a series of interviews, and we finally were able to have you graciously agree to do this. We want to be relaxed and comfortable, and I have a few questions, but just feel free to talk about anything you want to talk about.

Dr. Bud Frazier: Alright.

SP: You are absolutely a pioneer and an innovator. I'm going to go on and embarrass you a little bit. I mean, you've done more than 1,000 heart transplants, and you've led the way for the implantation of many left ventricular assist pumps and total artificial hearts. I've seen your work. I'm very impressed, and you're my hero.

BF: Well, thank you.

SP: But I think a lot of people will want to know, especially our younger generation, how did you become interested in doing what you're doing? How did that happen?

BF: Well, it was an evolution, like a lot of things. I went to medical school nearly as an afterthought. So it wasn't like those kids that grow up wanting to be a doctor. I thought it was a noble calling and still do and decided to go to medical school when I was actually was already graduating with my undergraduate degree. I went to Baylor, and Baylor at
that time had a policy of doing research work every year of your medical school. In fact, they gave you Tuesday and Thursday afternoon off to work on it, in your first and second year, basic science years. Literally by chance I ended up doing -- a friend of mine had designed an experiment doing kidney transplants in dogs to start out with. It's the last time I ever operated on dogs, by the way. But I had an experience with the department surgery and worked with Dr. [Michael] DeBakey and Dr. Jordan, and the next year I worked on the total heart with Domingo Liotta. That was my second year experiment, and of course the first two years were the ones you devoted the most of the time to. Then the clinical years were a little less intense, but the second year particularly I became interested in the idea of replacing the human heart, and of course in those days we thought, well, it's a pump, we should be able to do it. We were going to go to the moon. So this seemed like just a chip shot. I remember William Hall, a very good distinguished investigator, he was working with Domingo Liotta, telling me -- I think it was probably 1965. He said, “You know, Bud, by 1980 there will be 100,000 Americans with some form of artificial heart.” By 1980; and of course that didn’t occur, and tragically he himself died of heart failure after a failed heart transplant in the early 90s. So it’s always a bit gamey making predictions in medicine or nearly anything else. But it was that pump that resulted in the first implantation of a total artificial heart. That was a pump that Dr. [Denton] Cooley implanted in 1969 that we were working on, and it essentially, the pump he implanted was the same one we were working on in the lab. There weren’t a lot of changes. There were some. I think he changed the valve a little bit. Domingo Liotta did, and Domingo was, I think, the primary investigator on that particular project.

SP: Along those lines, in the early days what did you find as your greatest challenge? What difficulty? Was it regulatory? Was it mechanical? Blood surface?

BF: Well, depends at what level. You know, I think historically, in the early days what happened, as you know, the heart transplants came in late December of ’67. The problem with heart transplants -- Dr. Cooley did the first successful one in the United States. Not the first. I think Kantrowitz actually did the first.
SP: Yeah, he did.

BF: But Dr. Cooley, with the luck of the Irish, he did the first one that actually lived, and lived a year, a year and a half, and he ended up doing up a re-transplant on him, but actually the patient did very well. So, and there was a lot of hope for heart transplants, and a lot of concerns, of course, there being thousands and thousands of heart transplants done, I mean, and people didn’t realize the real limitation the donors would be. In the first 100 -- oh, I’m sorry -- the first two years, by the end of ’71, I think there were twenty-four patients alive after 171 had been done. The best data for that, by the way, is in a book called *Hearts* by Tommy Thompson.

SP: Oh, yes.

BF: He listed every transplant. That was something that couldn’t be done today, of course. But it’s listed in that book. In it is included a calf heart transplant that was done in India, putting a calf [heart] into the human -- Dr. Cooley actually put a ram’s heart and obviously those didn’t work very well.

SP: Couldn’t catch the pig?

BF: Yeah, that’s right. That’s right. The ram couldn’t run fast enough. So the general feeling was of discouragement in the field. Now, I think it’s important to remember that Dr. DeBakey did a lot of things, but the most important thing he did in this field was get funding for it, because this field would never exist without the NIH support. It’s impossible for these companies to do it with any sense of making a profit. It was just too intense of a leap to make, and Dr. DeBakey, from LBJ [President Lyndon B. Johnson] got -- he asked for a million, and he got $500,000 in 1964, which of course went a little further than it does today. So the project was already ongoing, and I think the barriers, the biological barriers, of course came later. I think the fact that we had the funding - 1973, I think they had, after heart transplants clearly had failed and been resigned to more or less an experimental role at Stanford and at the Medical College of Virginia, it really became
the interest to have a long-term implantable pump, and that was engendered by this
conference in '73 or '74. I don't think anyone's alive today that was at that conference, but
they of course recommended that the research be ongoing, and it was. I had the good
fortune -- I came back from the military in '70 and continued my training with Dr.
DeBakey and Dr. Cooley, and we, under the guidance of Jack Norman, who ran the lab,
they began working on a long-term implantable left ventricular assist device. I mean, it
was never envisioned as a bridge to transplant, as you know, because we weren't doing
transplants. It was envisioned as a substitute for transplants. And I think that the
bureaucracy entailed with that was a bit of a limitation in our advancing into the clinical
arena. It certainly wasn't an absolute, because we did. But it wasn't something that -- the
original RFP [request for proposal] was designed for a long-term pump. By long-term it
meant two years, and so I think that was a limitation also I think. When we designed it, of
course, I wasn't involved in designing the RFP, but just even putting a number on it, I
think, was a mistake. Of course, they needed to do that from a, I guess in their minds, from
a support, a design, an experimental design. But we had no idea how long it would last.

SP: Well, I know around 1975 or '76, I forget, but the rules changed, and the FDA came and
visited me and said "You really cannot continue to do what you're doing." In other words,
fabricating devices in the lab and then just putting the appropriate ones you think would
work in patients. So we basically -- it was a game changer, and I think it was probably
appropriate, but I mention this because I was going to ask you next, when do you make
the decision to go from the laboratory, from the animal experimentation, to the clinic?

BF: Well, you make the decision when you've gone through all the hoops, and there's only
so much can do in the experimental animal and in in vivo, in vitro experiments. So it is
important, I think, to do the background experiments first in the lab and then in vivo, and
I'd like to be able to do these things without doing the in vivo work, but we've nearly
never had a device that we didn't learn the limitations and had to alter it in vivo. The best
example of that was the first LVAD, the pneumatic LVAD. I was working on that with Jack
Norman and I was always interested in the pumps. I was always interested in that as a
career. Particularly, after I came back from Vietnam. I was sort of convinced I wanted to
try to do something, of long-term benefit and usefulness; and I’d always worked in these pumps, as I said, as a medical student and was involved, of course, with the intra-aortic balloon clinically. You know, these pumps were, to me, very appealing, but we learned a lot from the animal experiments. The most important thing -- I think there were two very important things we learned in the initial LVAD experience -- was the limitation of the inflow cannula. Now, we used calves, and the calves were a good experimental animal because they’re sort of a worst-case scenario. They’re growing and they have rapid expression of the problems they’re going to develop. There were two initial problems with the design. One, that it had to be totally implanted. That was part of the RFP, and it was a reasonable goal, but we couldn’t do that with a PULSA pump because the limitation -- and it had to last two years, I’m sorry. We had the limitation of the compliance chamber, because you can’t pump against a vacuum. So you have to have a compliance chamber. The longest we had a compliance chamber work was 203 days. Well, the device, you know, was supposed to work for at least two years. So -- and actually my contribution -- I had no contribution to make from an engineering standpoint, you know. I didn’t even like math growing up, you know. I was a history English major and so. But I did know we put these big tubes in the TB [tuberculosis] patient. We still saw a lot of TB at the VA hospital. So I knew that you could just vent it to the outside, just like you did a bronchopleural fistula, and I suggested that we just vent it because we couldn’t get the compliance chamber to work, and that was eventually the way it was implanted clinically. In spite of the fact -- and it was that suggestion that caused us not to be funded in ’82 -- I guess it was ’84 -- because we weren’t in compliance with our RFP by venting it. But the other very important thing we learned from animal experiments was the inflow cannula. You know, you have stasis in the inflow cannula throughout the duration of systole, which isn’t long, but blood normally doesn’t just stop in the normal circulation. In nearly all cases with these calves we’d have some degree of pannus formation on the inflow, and in several of them they would just stop the experiment altogether, and we didn’t have any good way of dealing with that. We tried to do fenestrations on the support, and actually they did even worse when we did that on the silicon support. So that was a big limitation. It was easier to put in with a long inlet cannula, you know, because you could move it and move that inlet around, but I made the suggestion that we should just shorten it, do away with the
inlet cannula, which we did. Now, Peer Portner never did with the Novacor, and I think what they had was -- you know, with the stasis. So they already had that stasis inherent in the Novacor. He also used sheep, which were a little more forgiving than the calf. I think that was one of the experimental animals that got away with it. But as you know, stroke was a big limiting factor in the Novacor, and I think it was all from that stasis in the inlet cannula and platelet aggregation et cetera and thrombus formation there. Well, micro emboli from the inlet cannula. So there’s two important findings. We would never have had a pump that worked if we didn’t make those alterations. Of course, one anecdote I love to tell because it’s seared into my memory -- I guess we can tell a few anecdotes in this thing. But when I was with Dr. DeBakey, Dr. DeBakey made a lot of great contributions, but he was like, as I’ve said many times, working under a Marine drill sergeant. He was tough, and he didn’t put up with any nonsense. We had a patient--I actually remember his name, but I guess we can’t say the names anymore--let’s call him just Mr. Jones, which wasn’t his name. Who we’d done multiple fem-pops [femoropopliteal bypass] on, and they kept occluding, and he had pretty good runoff from a popliteal bypass. He had a pretty good runoff so it was unclear why he was having the problem, but they finally after the sixth or seventh time, got him up to the floor, and I was an intern and covering on the floor. The nurse called me in the middle of the night and told me that, you know, Mr. Jones’ graft had clotted off again. So I had to go tell Dr. DeBakey, and I had been up all night the night before. I was covering two nights in a row, and I was very tired and a little bit daffy. I went to his office, because we always knew where he was, and this was around midnight and knocked on the door, and he came. I didn’t carry a beeper. There weren’t any beepers for Dr. DeBakey. You had to just personally tell him things. I had told him, I said, you know -- I think if I had said that Mr. Jones’ grafts had clotted off again, he would’ve probably fired me because he didn’t like information like that. But I had worked with him long enough I knew not to do that. So I said, “You know, Dr. DeBakey, I’m concerned about Mr. Jones. Would you please come see him?” So he was very grumbly and gruff and went up to see him, and of course his foot was cold. You never asked Dr. DeBakey questions because it was always trouble. You know, you just made him mad. He had so much to do. He didn’t want to have time to fool with you. But I was so tired, and in my mind I was saying, I wonder why this keeps clotting off. I said out loud, “You know, I
wonder why the graft keeps clotting off?” That really made him mad, and he said, "Come outside." That was rough. He would hit you. You know, hit you right in the chest. He hit me in the chest. "Why do you think it clots off? Have you ever heard of Virchow's triad? You know, Virchow's triad? When blood stops moving it clots. That's why it clotted off. The blood stopped moving. When blood stops moving it clots. Is that too hard for your pea brain?” he said. I said, "No, sir, I understand." He said, "Repeat after me." I had never heard him say that before. He said, “Repeat after me: when blood stops moving it clots.”

[Laughter] So I said, "Yes, sir. When blood stops moving it clots." He said, "That's right." Bam! He hit me again in the chest and walked off. But there's something about those teaching methods that's sort of seared in your memory. I think the inflow cannula problem -- I mean, there were a lot of very intelligent, educated, scientific people working on it, and they couldn't figure out a way to keep the inflow pannus from building up. I just remembered that when blood stops moving, it clots, and we just got rid of the inlet flow cannula, and that's why, you know, the pneumatic HeartMate was the first device to be approved, and we never had that problem with it, and we never anticoagulated, as you know, also. I mean, we could use it without anticoagulation for the pump.

SP: Aside from all the wonderful research and clinical applications that you've done, you also are very, very willing to share your knowledge and your information with others, which is not always the case, and I think the community owes you real thanks for doing things like that. You're very open and you're very willing to talk about your failures, even more so than your successes, which is very helpful. You're open-minded, and I'm leading into the next question, because we all grew up with pulsatile flow. There are many investigators and clinicians that were very resistant to thinking outside of the box. There are still some like that, but the difficulties with pulsatile flow assist devices with total hearts are fairly obvious until Dr. Richard Wampler came along with his continuous flow concept. You were very involved to support that concept. In fact, you were very involved to help Dr. [Robert] Jarvik convert his system into that. Would you say a few words about the history of that?
BF: Well, you know, knowledge is advanced by an *a priori* idea, and the idea you have to convert into some sort of practical experimentation and verification. The idea of an LVAD, for example, I think Dr. DeBakey always said he got -- when he realized that in the early days of heart surgery, when the mortality was so high, that if you just left some patients on the heart-lung machine for a while and rested it, sometimes they would recover. From that he went into the experiments of the pulsatile pump flow. Now, in the early on, I'd like to think it’s important to realize that we didn’t realize that pulsatile devices would have the limitations that they had. But, of course, you know, the heart beats 100,000 times every 24 hours, if you don’t do anything. So to have a pump that flexes 100,000 times every 24 hours and expect it to last for years and years was a bit of a jump. But in the early days, you know, it seemed promising, particularly with the Novacor. It had a very good durability, and it was only with time that we recognized that limitation. On the other hand, the size of it, I think, was my concern. As you know, at a capillary level, I can still remember those chick embryo studies where you could see the capillary blood flow was always very constant. There’s no pulsatility at the capillary level. So I’d always had an interest in this. I used to espouse it at ASAIO meetings, you know, the gyro-screw-loose guys, and they’re all meeting together at ASAIO. I remember I had a long debate with Glenn Pennington on pulsatile flow versus non-pulsatile, and I was the non-pulsatile. That’s why, you know, it ended up that both Wampler, who I actually didn’t know at the time, and Jarvik, who I knew but wasn’t working with him, anyway, stopped me in April of 1986 to show me their pumps. Because I had espoused this in, you know, numerous meetings. The one thing that at that time, early on, that was very appealing to me was the size. Because the size of these pumps, even the LVADs, sort of limited it to large people. We could squeeze it in some small people occasionally, but the patient’s size limitation of these pumps was a big limitation. I was looking at it as an LVAD. Its responsivity to inflow pressure, which makes it much like a normal [inaudible] response with continuous flow, had been known and observed for some time. But its role in balancing left and right flow, or its potential role in dealing with that difficult problem of right and left flow imbalance in the heart, was also particularly appealing to me. Following, you know -- actually, Rich Wampler showed me his pump, and as I said, and Jarvik at the same meeting, and I agreed to do research on it because I wasn’t confident that it would work. Because it’s spinning at
this very rapid RPM. I thought that particularly the hemopump might act more like a Waring blender for blood. You know, tearing the blood up, and it was so small that I thought it would thrombose. Again, showing the importance of in vivo studies. I mean, they’d done the in vitro studies at Rich’s company. It was called Nimbus. But they’d not done any in vivo, and we started doing the in vivo, and we found out in patients that it really didn’t cause hemolysis of -- or in the experimental animal it really didn’t cause hemolysis. Now, we started doing those experiments in the fall of ’86, and we actually implanted the hemopump in April of ’88. So this is very short compared to what today developmental phase. It worked perfectly. You know, just like we thought it would. Unloaded the ventricle of a patient who was mortally ill. He had advanced failure after a heart transplant, and we reversed it. We had a drug called OKT3 [muromonab-CD3] then that was very effective in reversing acute rejection, and he lived several years more and survived. I think that really was the Kitty Hawk of the whole field. You know, it showed us that it will really fly, and we just had to work on the details of it. It was spinning at 25,000 RPM, which intuitively you would think it actually would not have worked. Interestingly, you know, when he first told me, I thought he said 2,500 RPM. In Louisville in ’86. If he had said 25,000, I don’t know if I would have done it. But I thought 2,500 was a big jump. Billy Cohn, an associate, loves to tell the story that after we’d done several patients that I realized that it was really 25,000. When we were doing the experiments in the animal lab, you know, I had realized it was 25,000. By then we had already started, so, and we didn’t see any hemolysis.

[BF:] Now, similarly with Rob Jarvik, Rob’s made a great contribution, I think, with the blood-washed bearings. Prior to the work we did in the ’80s, the blood-washed bearings were considered not possible. You know, you had to have lubrication of the bearings. The first experiments we did, again, with Rob, he considered them failures, and in a sense they were. I was just happy that it worked. I think the first one worked for about three days before it stopped, and the next one hemolyzed like crazy. Rob would make these in his apartment in New York City, and he would send them down, and we would implant them in Houston. After they failed, we’d send them back. He’d make some alteration. A few months later we’d get another pump. We would implant that, and we went back and forth and back and forth, and Rob kept working, you know, diligently on this bearing problem.
But Rob confessed to me a few years ago that he probably wouldn’t have continued because he was discouraged by the experiments, because we did have problems with every one, but it seemed to be getting better. In fact it was. You know, the durability of the pump, et cetera. In April of ’88, when we did the hemopump experiment-- because I was working on both of these simultaneously, both these two pumps--he became encouraged when he showed that, you know, clinically, at least for the short term, the hemopump certainly worked clinically. It was much smaller than the Jarvik pump and much more traumatic. I think he said that encouraged him to continue. I do think, you know, these two events were really what ushered in the whole field of high-spinning pump and Wampler’s showed that you could tolerate such a physiology. Then, of course, Jarvik’s showing that you could actually have a blood-washed bearing. But the bearings aren’t perfect, and it’s nice to get rid of the bearings, but they worked a lot better than we even anticipated from the animal experiments. We’ve had patients now over eight years with these blood-washed bearings with the pump working without difficulties. So all of that, there was a bit of a serendipity to it, you know, and it was fortuitous that certainly both these companies - - Nimbus was certainly dependent a lot on NIH support with their projects. Although, this particular project, it wasn’t funded with NIH, and Rob, of course, had worked in Utah, and then moved to New York and did very valuable work in this field.

SP: But as you said, it was major leap of faith to break with the tradition of pulsatile flow and move to continuous flow. I mean you made the analogy at the capillary level where it’s important, but I wonder if either Dr. Jarvik or Dr. Wampler went to anyone else and asked them to help. I know you had a premier institute doing research, but you were just very willing to try it with your own time, at your own expense, and I just wonder if they were turned down, and I’ll have to ask them one of these days if they tried to approach anyone –

BF: Well, I can’t think of anybody that they would have approached. Maybe the Cleveland Clinic guys. But I just don’t know of anyone--you know, there just wasn’t a lot of clinicians involved in the field at the time, doing both the research and the clinical implantation. So I don’t suppose, you know, because, as I said, I knew Rob but we did not work together
closely. I was just an acquaintance of his, and I didn’t even know Rich. I couldn’t have picked him out of a lineup at the time.

SP: He was a student of mine when I was finishing my chief residency in cardiac, and he had idea after idea after idea.

BF: Yeah.

SP: I kept in touch with them, and I was amazed that he essentially gave up his medical career. I mean, he worked as a physician, but his primary goal was to develop this pump, which has changed the way we do things.

BF: Absolutely, and he’s a wonderful, wonderful man who made a lot of contributions. But I do think a lot of this was our having a lab. You know, I had a great lab, as you say, down there, and the lab allowed us to do things and rapidly transpose that into the clinical arena, and there were a lot of fortuitous circumstances. I have always felt -- you know, Claude Bernard used to, one of his mantras was to not to try to make conclusions about a given project but to try to decide whether you should do it or not. Then if you decide you should do it, design an experiment that will give you information relevant to whatever the project. But try not to make a conclusion just a priori. I started using the Bio-Medicus pump for long-term support. We had ECMO [extracorporeal membrane oxygenation] for long-term support. So we knew at least transitively you could tolerate this. Now, I think the other contribution I was able to make out of this was totally removing the heart. Now, that was another big jump, because in all these experiments we didn’t take over the circulation because you still had a beating heart in the circulation which engendered alteration in flow. Maybe not a pulse, but if the aortic valve doesn’t open, you don’t have a pulse, by and large, but you do have variation in flow. But if you totally remove the heart and replace that with continuous flow pumps, then there’s no pulse at all in the circulation. To me that was the -- really one of the most important things we did in our lab is showing that experimental animals can be perfectly normal, with not a trace of pulsatility or flow variation in the circulation, by removing the entire heart. And the first
experiment we did that with worked beautifully. Which was lucky because we’d done a lot since then, you know, that didn’t work out as well. You know, usually there’s some problem. It’s difficult to get these experimental animals through, but the first one did very well.

SP: Have you, I don’t want to say abandoned but basically put on the back burner, the pulsatile concept? I mean, if someone comes along with a miniature, very efficient pulsatile heart, I know you’d try it, because that’s you.

BF: No, I’d do the experiment, but I think there’re just certain limitations, and I think the biggest limitation is just the flexing membrane. We just don’t have material that’ll flex that long without breaking down. Now, saying that, the people at Symbion, which they have Nova patient out four years with one of these pumps, which I would’ve never thought possible. So I think, again, you have to do the experiment. You can’t make these a priori conclusions. You can have an a priori idea, but you can’t make that as a conclusion. You have to do the experiment and see what nature will tell you. To date they’ve lasted a lot longer, and there may be some way you can create a pulse; but once you do that, then you have the size limitation, and of course, that is also a problem. But I do think if, as you say, if somebody came with a small pump that was totally implantable that could be driven transcutaneously, which I think is something that is also very important that we need to be doing—or totally internally, you know, because we’ve studied a lot of plutonium work in the ’70s, and plutonium can work potentially for 87 years. So if we could do that, I’d certainly do the experiment and see what nature would tell. But it’s awfully hard now to do it as a long-term pump because of the normal limitation of membrane fatigue. Also, you need to be able to make it totally implantable like the AbioCor pump was, which I think was the best designed pulsatile pump. That was Bob Kung [phonetic] and the people at Abiomed did a wonderful job with that. But basilla [phonetic] was a large pump that had the membrane flexing problems, and that sort of thing.

SP: They’re trying to combine the biologic with mechanical. They are trying to grow membranes that’ll flex better. It’s hard to know what that outcome will be. Early on in the
80s we did some experimental work using magnetohydrodynamics, no moving parts, but trying to push blood around with magnets kind of worked on the bench. But actually our experiment just burned up one day.

BF: Yeah.

SP: But moving toward the continuous flow pump seemed to be at least number one for you at this point. Related to that whole industry, would you make a few comments on, one, the regulatory aspects of have they helped or hindered, and how would the corporate relationships affect this whole industry and effort?

BF: Well, there's two trap questions there, of course. [Laughter]

SP: You don't have to answer; we can erase them from the video.

BF: Well, I think the regulatory -- again, you know, things occur, particularly in that arena, as a reaction, and I think that the reaction -- it's Food and Drug Administration, isn't it?

SP: Yeah.

BF: It's not Food, Drug and Device. It's not FDDA. It's just FDA, and they became involved because of the excesses at the turn of the century, you know, particularly in foods. So I think it's certainly an appropriate regulation, a regulatory body. We certainly need to have that. Frankly, how they got involved with devices is Dr. Cooley put in the Wada valve. The Wada valve, you know, looked like a great advance because it opened –

SP: A little spiral?

BF: No, it was sort of a flat valve.

SP: [Inaudible].
BF: No, a lot of difference with the Bjork-Shiley, but it had a Delrin disk valve, and it looked great early on. It didn't have the occlusive, inherent occlusiveness of the ball valve. But after a few months that Delrin wore and it just popped out, and so it was a Cutter company. It was a company called Cutter. I'm not sure if they are still around or not, and it was called the Wada-Cutter valve. Juro Wada was involved in its design. As I said, it was a nice design, but they basically had done no in vivo experiments at all and not really any long-term durability in vitro experiments. When that became apparent, then they, you know, there was a hue and cry for some sort of regulation for devices, and that was '76 they got involved. The Wada valve, he started, I think, in '72. Early '70s, anyway. Then there was this feeling that there should be some sort of oversight, which I think is appropriate. Now, I think the problem in the original design--and I don't know that there were any medical personnel involved in the original FDA device interface--was to determine -- safety is something that you need to do as best you can in the experimental animal in the lab. But to determine efficacy -- the only way you can determine efficacy is, strictly speaking, if you have a baseline to go from. And if you're doing something that hadn't been done, again, if it's a new idea, you're feeling your way along a path. Well, if you're doing something new, you don't know the path. If it's something that's already been done, you know, you've got a pathway. So you can certainly do efficacy investigations on a new birth control pill or antihypertensive medication. But something that hadn’t been done before, how can you determine efficacy if you don’t have a baseline? I think, at least for recording, because there are things I know. You know, there's things -- memory clouds some things, but there's certain things that I, you know, I know firmly. The first device we approved was the pneumatic HeartMate implantable device. The first problem we had was how are we going to present to the FDA when we don’t have a control group, and I think Kurt Dasse and Vic Poirier did a great job, because they realized -- I put in the first twenty-two implantable LVADs in using the -- with the HeartMate. The Colombian Cleveland Clinic group started in '90, but I started in '86. But once we started, it became very popular because it worked very well, and we were getting a long transplant list, and we had the limitation of donors. We were using it as a bridge to transplant. But there were patients -- the entry criteria was just the hemodynamic measurements of very low cardiac
output and renal dysfunction, et cetera, but they had to be listed for transplant as well. We had a number of patients that met all of the criteria, but we simply didn’t have the pump, because the company at the time, you know, they could make one or two a month. But as it expanded, then there were a number of patients that simply the pump wasn’t available. So that acted as a -- statisticians have a word for it, a contemporaneous, sort of a nonrandomized group. They weren’t randomized, but they were contemporaneous, and they met all the criteria. The patients that we had -- I think we had forty-eight patients like that in the whole study that didn’t get the pump, and twelve of them were transplant. Of those twelve, five died early on. Seven lived. Now, of the thirty-six that met all the criteria, but when we went to put the pump in, we didn’t have it, I think the longest one lived about two and half weeks, and the rest were all dead usually within five days. So we had a -- and the ones that got the pump had a 70% survival of transplant, 138 day duration of support, and a 90% survival after transplant, which amazed me because I thought they would have a higher mortality after transplant because you had the pump and excess bleeding and that sort of thing. But in reality that was the best survival. It was a 90% survival. This is in the early ’90s. A one year survival. So I think that was our only real control group we’ve had in the LVAD field. We’ve had this REMATCH [Randomized Evaluation of Mechanical Assistance for Treatment of Congestive Heart Failure] trial, which I guess we did have a control with that, but it wasn’t a new pump. We already knew what the pump would do. It wasn’t like you were embarking on a new technology. We knew what the pump’s limitations were, and we knew what its durability potential was because we learned that from the bridge to transplant experience.

SP: Well, related to the bridge to transplant experience –

BF: So that was a limitation. The problem -- and regulatory remains so. As far as the companies, I think the problem with the companies, it’s not so much now, but certainly in the initiation of the field, there just wasn’t a product that was profitable. I think the first company to make a profit in the whole field was Thoratec, and that was in 1998, but Thoratec was formed in the ’70s, early ’70s. They’ve been around forever. So how can you have a company that goes more than twenty years without a profit? They couldn’t have
done that without the NIH support, and I think that's why, and there's no other country that could have done it. I think it was done in our country, and I think now it's certainly become lifesaving all around the world, these technologies. I mean, it's something just as Americans we can have some pride in, because that technology could've never developed. They put in over 100 pumps in Kazakhstan.

SP: Did they really?

BF: Yeah, I believe so. It's used around the world. But the system is laborious at times and frustrating at times, but it worked, and I think those regulators at the NIH who tried, and the FDA, you know, they tried their best, I think, to reach a balance between safety and making advances. Of course, the companies have to answer to their board, and they have to ultimately make a profit, but they couldn't have done it without working in conjunction, I think, with these federal initiatives.

SP: Well, you certainly have provided us with a wonderful history lesson related to the evolution of pumps. I mean, you started with the objective of a total artificial heart. Transplants sort of slowed that down. But when transplants didn't work, and we know there's zero positive life-saving with transplants. Someone has to die for someone else to live. Then we moved on to a combination of LVADs or BiVADs and total hearts. A big paradigm shift with the continuous flow pumps, which seem to be evolving and being very efficacious for use. Initially, the pumps were used as a bridge to transplant, that's what they were approved for, and you all did the first -- demonstrated that, didn't you?

BF: Well, no, actually. No, it was funny. We had done three bridges as transplants. We had done the first ones, and the pumps had already worked. We used an LVAD, an internal LVAD, in 1978. Cooley put in the first pump in '69 and another one in '82, the Akutsu heart in '82. In all those instances the pumps actually worked fine. We didn't have any surprises with the pump, but the only thing we had for transplantation was a pan-immunosuppressant, Imuran, and steroids, and the patients all died of sepsis. I think the first patient they began immunosuppressing him when they put the total heart in. So by
the time the transplant occurred, the white count was 2,000, and he died of overwhelming pseudomonas sepsis shortly afterward. Similarly, the second one was an LVAD, and we implanted it, and he was well supported with the LVAD, even though he had what we call a stone heart. He had no cardiac function. So without it -- and that was an interesting experiment for me because it demonstrated, you know, that with no cardiac function, just the left side, you could support the patient. But, again, he died. He lived a little longer. A couple of weeks, but died of overwhelming fungal sepsis, and the third patient died of fungal sepsis too. This was before -- it was '81 actually, before we had cyclosporin. But I implanted, transplanted a young girl in '84. In February of '84 she came in. She had a postpartum cardiomyopathy and she developed severe failure, and we put a balloon pump in. We supported her for about two weeks on a balloon pump, but her bilirubin rose to 30 something. She was still awake in spite of that. Had renal failure. She had positive blood cultures for both Streptococcus and Staphylococcus. Actually had written a note to me, [saying] "Let me die," on Thursday, and she had been on the pump, the balloon pump, for a couple of months by then. Then she did the same on a Friday. You know, her husband, I asked him what he thought. He said, "You know, we have two kids at home. Do everything you can, Doc. You know, whatever you can." But everybody was upset. The nurses were going to get a court order on the, you know, the next Monday, but we got a donor that Saturday, and we transplanted her. When we cut the heart out, it had a fungus ball in the heart. But, you know, it was a good heart, and we were treating her just with cyclosporine and plasmapheresis. You know, a low dose of IV cyclosporine, which, you know, one of its chief advantages, it spared the non-specific immune system. She actually - - we had acute cholecystitis the next week, and I took her gallbladder out, and she had a fungus ball in the gallbladder, you know. Well, we kept supporting her, and she got better and got better and got better, and about two months later she walked out of the hospital, and she had, you know, two positive blood cultures for bacteria and a fungus ball in her heart and her gallbladder. I asked her about the letter, by the way, as she was leaving. She said -- I asked her about her note she said, "What note?" "You wrote me a note, you know, before. You wanted me to let you die." She said, "I would have never written a note like that. I have two children at home. I never wrote a note." Of course, as you know, patients usually don't remember anything about the ICU experience, even though they seem
cognitive at the time. I worried about this when I was an intern. I used to talk to these patients afterwards that would come out of Dr. DeBakey's ICU, and they just don't remember. She said she remembered when they put the balloon pump in, the machine in her leg and when she went on the breathing machine. She said that the next thing she remembered was when she woke up after the transplant, which was about a two-month interval.

SP: That’s very typical.

BF: But in September of that year we had a meeting in Minneapolis on cyclosporine. You know, because that was the new thing, and of course Phil Lawyer [phonetic] was a great pal of mine, a great guy. I presented this case, and in it, I presented that I thought the limitations of bridge to transplant was in fact not the pumps but it was the immunosuppressive agent in these contaminated patients. Clearly contaminated with surgery and ICU, and with this device, and the sepsis risk was too high to justify it with Imuran and steroids. But with the cyclosporine that we’d transplanted this totally septic patient who survived, and that to me I thought it opened the door to reuse these pumps as a bridge to transplant again. Phil went back to Stanford, and that October they had a patient -- in fact, at that time, I think, that they were considering it with that patient. We’d been talking about it, because with both the Novacor and the TCI, in using it and just venting it to the outside. We had already decided to do that with the TCI, with the Novacor as well; and they went back and they implanted one. Now, they implanted intra-abdominally, and the colon ruptured shortly after they implanted it, but they were able to get a donor, and the patient lived, I think, nearly twenty years afterwards. So, again, the serendipity of this woman who lived another decade also. But I think these observations result in the experiment in a sense, and ultimately you have to have enough data that you can justify the use of these technologies in patients. By then we had plenty of data. We’d put the TCI in over 100 animals and similarly with the Novacor. They used sheep, as I said, but they had good long-term data with the Novacor. So the Novacor was the first pump, and it was done by Phil. From that experience they started putting it extra-peritoneal, which was another serendipitous sort of thing.
SP: Well, before we finish up, I’d like you to comment on one more question. We’ve reached the point now with the small devices, the continuous flow devices, they are proved for destination therapy, and it’s my impression that we’re right at the cusp of where we were in the early days of pacemakers. We know there’re about half a million people in the U.S. every year that have congestive heart failure that could probably benefit from some sort of device. The patients usually walk in with a bag of medicines. They’re in and out of the hospital repeatedly. An example might be Vice President Cheney. I don’t know if you want to comment on that experience, that kind of device. But do you think in the next ten years or so we’ll be putting in left ventricular assist pumps easily? Perhaps the cardiologist at some point will jump on the bandwagon and we’ll have people walking around with these devices almost as backup like, for example, defibrillators or pacemakers are?

BF: Well, I think, you know, the prediction of the future reminds me what Dr. Hall told me. I don’t think that’s what worked against him, but still it’s a bit gamey. But I’m much more optimistic now, and I’m optimistic because we did the experiment and nature’s told us this continuous flow can be a very advantageous and can be very useful. I think for the LVADs, we’re trying to make them smaller. I’m working on one that you can put in through the subclavian vein, thread across the septum and then bring a cannula out the small graft and sew it to the subclavian artery for early partial support of the failing heart, which I think we can justify. A very safe operation. We don’t have to open the chest and that sort of thing. I think that can be done. The technology’s there to do it right now. I think the other thing is a total heart replacement with a continuous flow pump. Now, I had done the first animal experiments, but I used two pumps. That’s all I had. We didn’t have engineering expertise in Houston. I always relied on people in California, Boston or Minneapolis for the engineering support. But I do think that the continuous flow total heart replacement would be a huge advantage, because in so many patients, as you know, we really do need to replace the heart, and we’re just dancing around it with the LVAD. This we’ve been working with a young man from Australia, Daniel Timms who’s been working for years on an active responding continuous flow total heart replacement. We’ve
done pilot studies on the animals, and we actually have an animal alive with it now, I mean, it's a pump smaller than my fist. The durability of these continuous flow pumps, as I said, has been very gratifying, and I think that with that -- the Cleveland Clinic is also working on similar technology -- that will be done. I think it can be done and will be done, and I think the beauty of the long-term durability and the advantage of size that you have with the continuous flow right now trumps the pulsatile pump for long-term support. As you know, the bridge to transplant is important for obvious individuals, in individual patients, but it still is statistically and epidemiologically really doesn't add much to addressing the afflictions. So I do think those things are going to advance the field and push it forward. I think we have to be cautious about it, because I do think the clinical sites involved need to be sites that have some commitment to the field and be a little cautious about being done sort of higgledy-piggledy in every community hospital. Saying that, of course, they said the same things about pacemakers. Although, I think as the technology advances and the safety of the technology advances and the physiologic problems that we have with the pump -- and I think this is very important to understand. The limitations of the pulsatile pump were in fact the pump itself, and the limitations of the -- I don't know -- the limitations of the continuous flow pump are not the pump itself but the secondary physiologic problem such as the certain amount of GI bleeding that we have with low pulsatility and the aortic valve problems. Now, this pump that we're working on and I think the continuous flow pumps, all the LVADs also need to induce a variability of RPM so that it will sort of wash out the heart and the pump as well, but mainly the heart, and I hope that will further be an advance and something that can be done and should be done. So I guess if we'd had this interview ten years ago, I don't think I would have been quite as optimistic as I am now, but time and the experiments of nature, again, has shown us that it's quite agreeable to this new physiology. Again, to remind everyone, these are not technologies right now that can be put in patients other than patients really facing the mortal outcome, and all the patients we implant are dealing with that problem. But I do think as the technology, particularly, as the safety of the technology improves, that one of the great advantages of this technology, in a sense resting the heart, will be recovery of the heart. You know the old-time treatment, George Burch and the old guys used to -- heart failure was treated by a bed rest. I think this will rest the heart, and I've had twenty-
four patients now that I’ve removed the pump from. Two of them I had to put it back in, but the others are still doing well, even with compromised EFs, you know, that can be treated medically. I do think in the future -- and you can see if either of us are around in a decade, see how it looks -- but I do think over the future as the device safety improves that we will more and more use these as bridges to recovery. I don’t like the term recovery, but a remission of the heart failure, to induce heart failure remission and remove the pump. As this becomes easier to do, safer to do, I think that will be a primary implementation of the technology. But, again, it's come a long way, and I was privileged to be involved from the very start, and have seen a lot blind alleys, and I think the key to our success has been the base support that we've derived both from the federal government and, I think, these companies. You know, all of us involved in the early days were sort of creatures of the Kennedy generation. You know, we thought we were going to cure world poverty and end all wars and go to the moon. Well, we did go to the moon but we also thought we would make an artificial heart, and I think we will.

SP: Well, this has been just a fascinating hour or so and a pleasure for me. Again, thank you; thank you so much.

BF: It’s always fun, Steve. Thank you for all you do.

SP: Alright. Dr. Frazier, as we wrap up, would you just summarize your life and your experience, in two or three minutes, over your work?

BF: Well, I had the good fortune of being involved with early pioneers in the field of cardiac surgery and seeing the advances and how they were made and how they were applied. Sometimes with boldness and sometimes someone might be critical of it, but the only way you can move forward is by moving forward. You can’t move forward looking backward, and I think that’s one of the things that I’ve certainly learned in my years in this field. We’ve seen the pumps evolve from the temporary pumps that Dr. DeBakey first implanted in the ’60s to long-term pumps that now last greater than eight years. We have patients with these pumps in greater than eight years, doing well, and restored not only to
life but to an active, meaningful life. The advances have chiefly been made in assist devices. We've had a limitation with the total heart replacement, and with miniaturization of these devices and simplification as far as their surgical application and implementation. But I think both of those fields are being addressed now, and I think they hold a very promising future with the experimental models that we have using something, for example, like a 3-D printer, which we can make iteration after iteration of designs and test them in a short amount of time that in the past would, in the development of the field, would take months to do. I think this will be a very important tool in advancing the field, and I am confident that within the very near future we'll have totally implantable pumps, transcutaneously powered. Again, perhaps we can look, as we did in the '70s, with plutonium powering. But certainly transcutaneous powering can be implemented now, and I think we will have a transcutaneously powered total heart replacement in the future with the continuous flow pumps. I think they hold the most promise because of their advantage not only of size but of durability. So I'm hopeful that there're young enthusiastic surgeons and medical investigators and scientific investigators that will take this challenge and continue to move this important and life-saving field forward.

SP: Wonderful. Thank you, again.

BF: Thank you, Steve.

[Interview ends]