Dr. Charles McIntosh Oral History

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Spring 2009

SJ: We're here today in the FDA History Office with Dr. Charles McIntosh. We're going to talk about the history of heart valves, heart valve creation, testing, and regulation.

CM: Thank you, Suzanne. Well, there are other things that we did at the NIH as well. We not only worked on devices, but we invented operations. But the thing that's sort of important to know is that back in the early '60s, if we were to get information about how a patient's heart was functioning, we relied primarily upon cardiac catheterization, where we'd measure pressures to determine the amount of obstruction, we'd do angiograms to determine the amount of leakage from a valve, we would provoke some gradient screen as a change in pressure across a valve, and what have you. And most of that data was sort of unique in the early days of cardiac surgery.

There were a lot of other institutions that were doing cardiac surgery at that time. The thing that's most unique about the NIH, I think, is that we had all of our patients come back in about six months after their operation to see (1) clinically how they were doing, and (2) we probably did cardiac catheterization in 95 percent of our patients who came back, which is very unique. Outside of the NIH, people would have to pay for it, or the insurance and what have you, but the NIH used to pay to have the patients come back, their transportation. And then we would see them in the clinic on a yearly basis and, if necessary, repeat a cardiac catheterization.

Now, that had a number of values. One is it told us if we changed pressures in the heart by putting in a heart valve. And in the beginning, the heart valves had so many problems associated with them in terms of either chewing up the blood or hemolysis, or forming clots on the valves and causing a stroke in the patient, that we kept looking for the ideal time to intervene. You didn't want to put a heart valve in too soon if it was going to cause the patient to have a stroke. And some patients, for example, with aortic regurgitation, we would allow their hearts to get rather large, and some patients would recover and have good symptomatic improvement, but some wouldn't. So, one of the things that we did, we worked very closely with the Cardiology Department at NIH. Steve Epstein, and Bob [Robert] Balaban, who is immediate past-president of the American Heart Association, and I worked very closely: When should we intervene in somebody with aortic insufficiency? And he was studying the echocardiography, if you would, of what would happen if we waited until certain dimensions were exceeded. Would that patient be less likely to have a benefit from their operation, or would they derive a good clinical benefit from it? So it was the timing of the operation that we were interested in until we had better heart valves. And, fortunately, better heart valves came probably about a decade after we started doing this.

SJ: What valves were you working with?

CM: Well, the first heart valve that was designed there was Nina Braunwald's. She was the first female cardiac surgeon in the world.

SJ: Did you work with her?

CM: I came the year that she left. She and Dr. [Eugene] Braunwald, who's now at Harvard, left the same year I came, in 1968. But Dr. Braunwald's contribution was she made a bi-leaflet valve out of, I believe it was Teflon, which had what looks like umbilical tapes attached to it, that she would bring outside of the ventricle, tie them over a button, so it actually mimicked what the mitral valve looked like, including the cording, which are the strings that hold the valve in place. That was her primary contribution, I think. Dr. Bob Reese, whose place I took when I came there as an attending, worked on the Hancock-Jaffe bioprosthetic valve.

But the other thing that we did—and let me just get back to the points that I was making about the importance of the catheterization—is that we would be able to evaluate what hemodynamic improvement the patient had with replacement of the valve. Were we able to lower pressures in chambers? Were we able to get rid of gradients? And that was very important hard data to get because I think a lot of people in the world really relied upon the NIH for that information.

And we didn't test all the heart valves that came along because—I don't know if you've seen the display case at the NIH, but we have probably 50 or 60 valves in there, most of which failed.

One of the first valves that really worked and we really put a lot of trust into was the Starr-Edwards ball valve, and that was made by Dr. Albert Starr, who was a cardiac surgeon at Oregon, and Mr. [Lowell] Edwards, who was an engineer. They worked together. And it was essentially a ball made out of silicone rubber inside of a cage, and it acts somewhat like a ball and [unclear] it goes up and down with systole and diastole of the heart. The first ones that we used were—and they all were identified by certain series—the series 1000 represented the aortic valve; the series 6000 represented the mitral valves. And the problem that we had with the aortic valves in that first series is that we didn't really know how to cure the silicone that was used for the rubber ball, and the patients, some of them, would develop a condition called ball variance where they would actually absorb lipids from the blood into the silicone rubber, and then the ball would either erode on the outside, become smaller, and potentially could go out between one of the three struts, or it increased in size and could potentially become stuck. They also were known to crack, and sometimes they would split in two and the ball would just embolize out of there. And that, again, was because we didn't know the best cure process for the silicone.

We had a number of patients that had ball bearings, and there wasn't any other way we could determine it. Catheterization wouldn't show us, plain x-ray wouldn't show us, angiogram wouldn't show it, pressure changes with time wouldn't show it. So I took the problem to one of the bioengineers at the NIH, William Schuette [Biomedical Engineering and Implementation Branch], and Bill and I sat down and looked at the problem, and Bill was able to come up with a test that we were able to measure excursion, if you would, of the ball, and we knew normally what it should be, and it was plus or minus 5 percent from that. We would see the patient had ball bearings, and oftentimes they'd get operated on for just that information. But in the course of about 10 years, we probably went through four or five

different series of Starr-Edwards ball valves. They changed the cure process of the silicone rubber, and that solved the problem of ball bearings. And those valves, I'm not sure if they're still sold, but a lot of people are still implanted with those valves and they're working very well.

SJ: In the United States, or in the world?

CM: In the world; primarily in the United States, yes.

SJ: That's what I thought.

CM: Yes.

SJ: You mentioned the Biomedical Engineering and Implementation Branch. Is that who you were working with?

CM: Yes.

SJ: Okay. Is there anything that we need to know about that particular branch and the kind of work they were doing? Someone had suggested I ask about it.

CM: Well, the work that I described with Mr. Schuette was certainly a good example. Unfortunately, he died about four years ago, and I don't know who else has been working there. I know that Kenny Kempner, who is in the IT section of NIH, has been very much involved with automation of care rooms and things like that, and electrocardiograms. But in terms of development of heart valves or tests that we used on them, it was primarily bioengineering, and Bill Schuette got involved with that.

As I mentioned before, the Starr-Edwards ball valves had a, you had to put a patient on Coumadin for lifetime because the materials they were using were thrombogenic in some patients. And the stroke rate on patients with the Starr-Edwards 1000/6000 series valves was upwards of 10 to 15 percent, which was unacceptable. So one of the things that we've done to take care of the ball-bearings problem indefinitely, is the ball was changed to a stellite 21, which is 21 elements in a hollow ball that had the same specific gravity, if you would, of blood. That ball was not going to absorb any lipids. The problem is it was rather noisy. So the valve was then covered in fabric, the same fabric they used in the sewing ring, with the hope that the cells from the heart and from the surrounding tissue would grow into this material and, one, soften the amount of noise, but, more importantly, to put a tissue covering, if you

would, over the struts and the sewing ring in the valve that would be less thrombogenic. Well, that solved one problem.

Now, the next problem that we then solved was that, because of the beating of the ball against the sewing ring in either the aortic or the mitral position caused the fabric to tear, had become fragmented, you know, we had all these little fingers of Teflon sticking up that were thrombogenic, so the next thing was they went around the base of the sewing rings and they placed little nubs on there so the ball would seat on metal rather than on the fabric, and that solved the problem with cloth wear around the orifice. But then we found out that, given enough times of the ball going up and down, it would wear the cloth off the side of the struts as well. So Starr-Edwards then came out with a valve that had not only the metal struts around the base, but a strip of metal on the inside of the struts so the ball would go up and down on these metal tracks. And, again, they were a little bit noisy at that time.

A little bit later, probably about 1970 or so, the bi-leaflet valves came out, which were the low-profile valves, and that was a very important thing because when you put a ball in a cage, either in the aorta or in the mitral position, it takes up a fair amount of space, and so you have to size it accordingly so that you leave room for the blood to go around the ball. The concept of a bi-leaflet valve, or even of a tilting-disk valve, solved that problem in that the area around the valve itself was not impaired by the size of the ball. And the one that became probably the most used, the Bjork-Shiley valve, that we used for a long time, had a disk in it that was bi-concaved, and that worked fine. And then for some reason, because of the flow characteristics, they went to a convex or concave valve, the Bjork-Shiley. Maybe you're familiar with some of the problems that resulted with that in that the hinge began to fracture.

SJ: From what I understand, the original valves were carved out of single pieces of metal, whatever metal they were using. And then they developed a new metal that they thought was superior; especially, it resisted thrombosis or whatever. And Shiley was the first to be welded, have welded struts?

CM: Yes. And what happened . . .

SJ: And that turned out to be the key problem?

CM: Yes, because they were bending back the hinge, some of the assemblers were bending back the hinge to insert the disk, and then closing it. In fact, I was the chairman of the circulatory systems panel, and that issue came up and came to a panel hearing.

SJ: So it was a quality-control issue?

CM: Yes.

SJ: Ah, that's not what I've heard before. I thought all of the valves had—it was an engineering problem.

CM: It was a manufacturing problem. But what did come along with the Bjork-Shiley valve, then later the St. Jude valve, was the use of pyrolytic carbon, which was very, very resistant to thrombogenesis. And those valves have served very well. In fact, the St. Jude's valve is essentially the same one today that was used 30 years ago. I think the Bjork-Shiley valve, the bi-concave, is no longer sold, but I'm not certain of that.

But the drawback is that mechanical valves were all quite durable, but they required lifetime anticoagulation, and that has its own problems associated with that.

So in about 1970, Dr. Reese started working with Hancock Laboratories in California on a bioprosthetic device, and the first ones that were manufactured and tested were actually treated with formaldehyde, and that did not work well. That broke down very quickly, and patients . . . I think that was only on the market for about six months.

But then they got into the glutahyde fixation, which is another member of the aldehyde family, but it tanned the valves in an entirely different way. These are usually pig valves. They're tanned in this glutaraldehyde. The problems that we saw in the '70s with them is that they had a tendency to accumulate calcium, or they had a tendency to fracture after a period of time. But unlike the mechanical valves, if the tissue valves failed, they usually did it in a way that didn't kill the patient. They'd come in with a new heart murmur, new symptoms, and then if we could cap them and find out the valve had become stenotic with regurgitation, we could usually operate on them safely and not as an emergency like if a mechanical valve begins to thrombose off.

So, over the years now, this whole process of how the valves are tanned and the agents they now have essentially eliminated calcification of the valve, and most patients will not require lifelong anticoagulation with Coumadin with a tissue valve, which is a real plus. And they're quiet.

SJ: But they don't last as long as the mechanical ones.

CM: Well, they don't last long, but the quality of life for the patient is much better.

I mean, I had one example, a classic example, was that Dr. [Andrew "Glenn"] Morrow, who was chief of the department, was very reluctant to put the tissue valves [unclear] every year. And every five years, we'd make a presentation to either the Society of Thoracic Surgeons or one of the other thoracic groups. And finally we had pretty good confidence, if they didn't use them in fairly young people, they held up pretty well. So we would use them in individuals 60 years and older.

But I had a young man that had a long history at the NIH who came to Bethesda early on to have a bicuspid aortic valve repaired by Dr. Morrow, and he opened the valve up. And he came back probably 10 years after that, and the thing had become fibrotic and calcified again. So I operated on him, and I

put a tissue valve in, and he was very happy with this. Well, unfortunately, about 10 years after that he came back, and the valve had now calcified. And Dr. Morrow said, "Under no circumstances are you going to put another tissue valve in him; he's going to get a mechanical valve." And I didn't say anything.

So I went over to see the patient, and he said, "Dr. McIntosh, why are you talking to me about a mechanical valve? I want to show you why I'm having this done." And he had an old eight-track tape that he put into his bedside, and there was a picture of him doing rapids in whitewater rafting with a helmet on, and, of course, he couldn't be on Coumadin to do that. He said, "This is the only reason I want to live, is so I can continue to whitewater raft." So I put . . .

SJ: Wait a minute. Why couldn't he do it with Coumadin?

CM: Well, if he hit his head, he'd have an intracerebral bleed.

SJ: Right, sorry.

CM: And so I went back and told Glenn, "You go over and talk to him. But," I said, "he's not going to have a mechanical valve," and I told him why. And Dr. Morrow's usual response was, "Nhhh." So I put another porcine valve in, and the patient knew that he may have to have that replaced at some time. But the quality of life he had was quite good.

Now, with all of the nuances of anti-calcification methods and the glutaraldehyde fixation and the new sewing rings, there have been a whole series of valves made out of both the porcine valve from the pig as well as the pericardium from the pig. And they almost last—I've had patients now that are 30 years out with their porcine valve. So, some patients still can wear them for a long time.

SJ: I got a tour of Edwards Scientific Labs in California. I've never seen anything like it. I mean, they take the tissue and they map it, essentially, and they get the best, the absolute, everything is the exact same thickness. You know, I think they're aiming for the fairly thick pieces. And the women sew these things in their microscopes, and it was really better than nature. I remember saying to my uncle, it's really amazing to watch them put the porcine valves together.

CM: Well, it's interesting because Cook Medical, who I work for now, is developing a valve for deep venous insufficiency, and we've been working with the Hancock Jaffe Laboratories, with Dr. [Norman] Jaffe. He's been dealing with tissue valves for 25 years. We've talked about this because when you go back and look at the rejection rate for just valves which are heart [unclear] pigs, you only get about a 15 percent yield. They throw 85 percent of them away. They can tell by looking at the range from the collagen and what have you whether it's a good valve for fixation or not. And they're doing the same thing now, we're using just a single [unclear] from the aortic valve. But it's a science and an art.

But the thing that was, I think, the world relied upon was that NIH, I think, presented unbiased data from our angiograph findings and our hemodynamic findings and what have you.

The other thing that was wonderful about the NIH is that the operating room, which is that circular building, had a central portion that was set up just for monitoring of the two operating rooms that we had. We could do any catheterization maneuver in the operating room following an operation that the cardiologists could do in the cath lab. We couldn't do any angiography because we didn't have the imaging equipment in there. But we could measure gradients; we could make sure, if we had a child, that the hole was closed in the tetralogy of Fallot and that there was no residual shunt, that there was no obstruction across the outflow track of the right ventricle.

SJ: And you could do that while they were still asleep?

CM: Oh, yes.

SJ: So that caused a lot less discomfort.

CM: Oh, yeah, absolutely.

But we used to do what's called closed mitral commissurotomy, an operation that was developed in the 1940s, and we continue to do them because we can get excellent results with it. We could measure with our finger whether we had regurgitation, and then after that you could put needles into the left atrium and the left ventricle and you could actually measure the pressure drop across the valve to show whether it would open adequately or not. So we knew before we left the operating room. And we didn't use the heart-lung machine for this because we knew that we either fixed the valve or we created a problem. So then we'd just have to go on to the next step.

So it's having that kind of ability to measure pressures in the operating room that really made the NIH the benchmark, if you would, in terms of hemodynamic data.

SJ: And that would take care of two factors, I would presume. One is the valve itself, and the other is the operating techniques?

CM: Yes.

SJ: In other words, if you were at that point able to determine over time if it was the valve or if there were techniques that need to be tweaked or some that were more successful than others.

CM: That's correct. And a lot of people used to say, "Well, how can you even ask a patient for a second catheterization in six months?"

But a number of times, patients would come back in six months and say, "I'm not really doing well." And we'd cath and we knew exactly what had happened to the pressures in the lungs or the left atrium or the left ventricle, wherever it may be.

And if five or six years later they come back and say, "I'm really not feeling well. I'm beginning to feel the same way I did before I had the valve replaced," we could repeat the catheterization, which we did. Then, if the numbers matched what they were when the patient was feeling well in six months, we said, "Well, it's not your heart. The valve is still functioning well. Your coronary arteries are normal," and what have you. So that was a real plus for the patients because we had numbers.

And I said yesterday, Glenn Morrow's saying was, "If you can assign numbers to it, we can talk about it. We can't talk about anything other than numbers." So we knew what we could advise the patients. Sometimes they just had to be tuned up, medication and what have you.

SJ: But you were doing clinical trials, or was this more of a treatment program?

CM: This was a longitudinal database, if you would, for all of congenital and developed heart disease we operated on. We didn't do transplants at the NIH. We didn't do the really complex congenital cases like the core [unclear] or transposition or some of those, but we did a lot of tetralogies and other things.

And it was, again, the ability to be able to do what's called "indicator dilution dye curves" in the operating room, so we could tell whether there was residual shunt after we put a patch and closed a hole in the atrium or in the ventricle. We could measure pressure gradients across the right ventricular outflow track and make sure we relieved all the obstruction. So that was a real boon for us to be able to do that.

Now, one of the things that changed a lot of this was the advent of ultrasound, and there was early . . .

SJ: When was that, roughly?

CM: You know, I'd have to look back. I'd like to say it was probably in the mid-1970s, because a couple of the engineers at NIH came to me with the first two-dimensional ultrasound and said to me, "What do you think of this?"

And I said, "Well, you know, we have so much data now, catheterization and angiography and so forth." I said, "I don't think there's going to be any real value of ultrasound." I've told that story, and it taught me a lesson early on to never discard something. Now it's the way we look at most things. And I went from the 2D to the more automated 3D.

But we used to do echoes in the, ultrasounds in the operating room.

One of the operations that the NIH was famous for was the operation for obstructive cardiomyopathy, and we would measure, we would actually do an ultrasound by putting the probe directly on the heart to see exactly where the contact point, what had caused the obstruction. And then, after the operation, we would do a repeat echo in the operating room to make sure that the valve leaflet was now moving in the direction it's supposed to, that the obstruction was gone, and that we had not created an opening by taking out this piece of muscle. So we'd take out a piece of muscle about the size of my little finger right underneath the aortic valve.

SJ: Okay.

CM: And it's all done just by three incisions: one vertical, two vertical, and one horizontal, and it was blind. There was no way you could see what you were doing.

SJ: You had to feel it.

CM: Well, you had to think you were in the right position. It was a character-building operation. And Dr. Morrow actually created that operation. It was called the Morrow procedure. And he died in 1984, and I probably did 125 Morrow procedures after his death. And it was character building. I mean, you never took any of those things for granted.

But, again . . .

SJ: And the purpose of it?

CM: Was to relieve the obstruction.

What happened to patients with hypertrophic cardiomyopathy is that their septum, which is normally about a centimeter thick, may be two, two and a half centimeters thick, and there may be a bulge in the septum on the left side. Normally, when the left ventricle contracts, the anterior leaflet of the mitral valve goes posteriorly so that blood can get out of the outflow and back to the left ventricle. In patients that have this bulge in here, there's a Venturi effect, it was called, and so when the ventricle contracts, the Venturi effect draws the anterior leaflet of the mitral valve against the septum, and it causes the obstruction, and people would faint. Some of them died. So, once you created this channel behind the mitral valve, it reduced the amount of Venturi effect, and now the valve would go posteriorly again, where it was supposed to be.

And that operation, many patients came from all over the world to have Dr. Morrow perform that operation on them.

But I think it was the evaluation of the use of the ultrasounds, a lot of the techniques in terms of what do you have to know in terms of velocities and things like that. Some of that pivotal work was done at the NIH in the Department of Cardiology. And I think that was one of the roles that the NIH continued to play because we started to do a comparison between reliability of ultrasound compared to angiographic and to hemodynamic data. So we could say, well, in the beginning we saved maybe 25 percent of the data derived from ultrasound was good, 25 percent was bad, and 50 percent was questionable. But the technology has now become so refined that most people will go to ultrasound and not necessarily rely upon a catheterization, unless you're looking at the coronary arteries, and now there are other techniques you can use even for the coronary arteries.

SJ: In order to allow these surgeries to take place, there were some advances in other kinds of equipment, the heart-lung machine and things like that, that helped facilitate both safety and efficacy of the operation. Can you talk just a little bit about what you observed and what you found most useful?

CM: I think I mentioned to you yesterday that when I was a junior in undergraduate school, which was a long time ago, I went to the Mayo Foundation for a spring break, just spent four days up in the St. Francis Department of Pathology. And I wandered into a laboratory one day where they were working on an animal, and they had the animal hooked up with canulae coming out of the femoral artery and vein, hooked up to this large, rectangular plastic case that had platinum screens, and the blood would pump up to the top of it, then the blood would tumble over the screen, and in that process it was aerated with oxygen and gave off carbon dioxide, and that was one of the first beginnings of the Gibbons heart-lung machine.

When I first came to the NIH in 1968, we were using a disk oxygenator for an adult. It was about 18 inches, two feet long, I guess, and it had a hundred stainless steel plates in it that had sort of a, not a curved surface, but sort of a rippled surface in it. And the cylinders would revolve around, and the blood would come back into the patient and be picked up in these cylinders, and the same thing would happen, it would be oxygenated. That device was a very sophisticated device. We had sensors that could sense whether we were getting blood back in the patient or the patient was losing blood somewhere, and it would adjust automatically so the volume would stay constant. It was very gentle on the blood. I had patients on bypass for sometimes six, seven hours with no hemolysis of the blood, which speaks a lot about that device.

And then the bubble oxygenator became more popular. It didn't require . . .

SJ: Where did the one you were talking about after Gibbons, where did . . .

CM: That came from Minnesota. That was the . . .

SJ: Medtronic?

CM: No. That was by a small lab.

SJ: Oh, at the University of Minnesota.

CM: Yeah, exactly.

SJ: Another one of those sort of hand-manufactured small pieces.

CM: Exactly.

SJ: Yeah.

CM: In fact, I think I may still have the pediatric model.

The real disadvantage of this adult model is that we had to use five whole units of blood to prime the pump, which meant that, one, the donor was an issue, and, secondly, in the middle of all this we began to learn about something called hepatitis C, and some of that may have been transmitted by these multi-transfusions. So when the bubble oxygenator came along, you didn't have to use blood to prime it. You could use other solutions. So hepatitis and eventually AIDS and so forth became a nonissue with the bubble oxygenator.

At the same time . . .

SJ: Who made the bubble oxygenator?

CM: That was made by a number of companies, some of them were co-made.

SJ: And how rare were these machines when NIH got one?

CM: By the time we got most of them, we had gone through the FDA process and were approved, and we started using them.

But the other great asset we had at the NIH was Dr. Ted [Theodor] Kolobow, who invented the membrane oxygenator.

SJ: How do you spell that, C-o-b-b-l-e?

CM: It's K, Ted Kolobow.

SJ: K.

CM: Yeah.

Ted has recently retired, but he came up with this idea of wrapping a membrane, if you would, that was very, very gentle on the blood. And, in fact, it was the device of choice, and still is, for ECMO, which is the extracorporeal circulation used on some children and some adults who are having ongoing failure. And Dr. Kolobow, I used to work on some of those patients back in the late 1960s who were in the cardiac surgical program, who worked with the product development section under Dr. Robert Bowman at NHLBI. And they had to have people who would sit up all night with patients, and that usually fell to the clinical associates, to the clinical surgery, which would have been me in 1968 to 1970. So I had the pleasure of working with him at that time. And that is, obviously, a big step forward.

And, of course, now things are being done off pump, where the heart-lung machine is not even used—again, trying to minimize the neurological effects that cardiopulmonary bypass may have on a patient.

And also, cardiac surgeons are attempting to do things through smaller and smaller incisions to try and keep up with the cardiologists who are doing things through a stick in the groin, and that's all. And no matter how you slice it, an 18-gauge or 20-gauge needle in the groin or a 12 French catheter, or 5 French, is a lot less than anything that a surgeon can do through a sternotomy. So there have been a lot of very interesting things that have occurred that have made, not just valve replacement, but all operations, I think, much safer for people.

And now, with the advent of endovascular therapy, where things, such as repair of aneurysms and aortic dissections and things like that, are treated by using a 20 French catheter with a whole Dacron device with stents in it being put in through a small cutdown in the femoral artery where patients go home within two days' time, and usually are not on a ventilator and don't spend time in an ICU, don't receive blood products. The whole paradigm has shifted, and I think it's for the better.

I don't know if NIH is currently working on any endovascular therapy.

I'm sure that in the beginning, Dr. Goldman got very much involved with Dr. Braunwald.

SJ: Let's go back, and for someone like me, who's not acquainted with the organization and NIH, and then we'll get to FDA and that kind of thing later. But show me a picture of how big the group was, what the group looked like, the other interactions.

CT: Dr. [Robert] Bowman probably had 12 or 15 people in his division or unit.

SJ: Which was the [NHLBI] Laboratory of Technical Development?

CT: Yes.

SJ: Right.

CT: When I was there. Dr. Kolobow was in that unit. There were several other physicians, and I remember people that were machinists who were skilled with all kinds of metalworking tools. It was a playground; that's the only way you can describe it. In fact, Dr. Bowman and three or four of his colleagues would meet in the dump in Rockville every Saturday, and they would look for things, motors and gauges and things like that, and he'd bring it back. And he'd walk into his office, and he had all these things scattered across his desk.

SJ: Do you know when Bowman came to NIH?

CM: He was there before I was. He was probably there in the early 1960s.

SJ: And he would have worked with Nina Braunwald?

CM: I think he probably did.

SJ: Where was she when she was in NIH?

CM: NHLBI. She was in the Clinic of Surgery. She interviewed me when I came to interview as a clinical associate, which was in 1966.

But Bob [Bowman] got involved with a lot of product development, I think, for the cardiologists. If they were trying to miniaturize transducers or put a transducer on the end of a catheter and things like that, he'd very much get involved with that. I don't know what his role might have been with Nina Braunwald, and I don't think that he necessarily worked with Dr. Reese with Hancock Laboratories. But I think we probably discussed some of the problems we saw in the early generations of the Starr-Edwards ball valve with him. But, I mean, it was a technology group that you just had no idea what they were working on.

And I think Dr. Bowman, long before the angioplasty balloon and things like that, he was thinking about, how can we treat these plaques, if not in the heart, at least in the peripheral arteries?

SJ: There was someone in NIH that worked on that. His papers are at the National Library of Medicine. I'll look it up.

CM: Okay.

SJ: But his papers are in the National Library of Medicine, and he was working on valves for other parts of the body. What do you call that?

CM: Well, for vascular insufficiency.

SJ: Yes, exactly, exactly.

CM: Right.

SJ: And they called it a valve, but that was what was confusing. They have the papers in the wrong—they talked about heart valves, but they weren't heart valves at all.

CM: No. They were probably semilunar valves, which you find in the venous system. For example, we have about 80….

SJ: They just go one—well, they're not leaflet valves.

CM: They are leaflet.

SJ: They are leaflet.

CM: They are, but they're very small and very thin.

We have probably about 80 percent of the valves in the lower layer below the knee. Then you have the deep venous system above the knee up to the groin, and there are probably four or five venous valves. If a patient developed deep venous thrombosis, and the inflammation of the femoral vein in the leaflets, they then develop a regurgitation, if you would, and that causes the swelling and the pain and the ulcers that you see in patients with [unclear] DVT. But those are semilunar valves.

And, as I said earlier, we're currently working on one now that's taking a single [unclear] from a pig and putting it in a frame and implanting it into the deep venous system.

SJ: Well, were there physicians that were tinkering in the lab, other than Bowman, and did you ever tinker with creating a valve or doing anything like that, or by the time you came along, were people…

CM: There were people that were a lot smarter than I was that knew how to do that.

SJ: Okay.

CM: What I was working with at that time was being able to develop a framework, if you would, in patients, particularly children, with aortic insufficiency so we could avoid a valve replacement by putting in three sort of U-shaped devices in the cusp of the aortic valve so we could have a constant size and they wouldn't separate. These were all put in, individual sized, and then we would actually suture them together. So it was—I did some work with Bob, but most of the work that was done there was not done by me.

SJ: So that answers the question. But it must have been—well, you said it's a playground. It must have been very exciting to see what ideas people came up with.

CM: I got on the elevator one morning with Dr. Bowman and I said, "Bob, what are you working on?" He said, "I'm trying to make kamikaze worms for blasting out the coronary arteries."

SJ: Make what?

CM: Kamikaze worms.

SJ: Worms?

CM: Worms, yeah. You can put C4 in worms. That's the kind of thing he'd say to you. Or you'd talk to Dr. Kolobow, and I said, "Ted, what are you working on?" "We're working on an alternative to breathing." And I would just kind of look at him and I'd think, "Okay, I'll wait till the paper comes out. Maybe I'll understand."

SJ: Some days you don't know if they're kidding or not.

CM: No, they weren't kidding.

SJ: They were never kidding?

CM: They were never kidding.

SJ: Oh, geez. I like the worms.

CM: Well, you know, when the angioplasty catheters came along, that essentially was like forcing it out like an explosion.

SJ: Let's see. I don't want to get caught here.

I wanted to ask, Dr. McIntosh, about Ted [Theodore] Cooper, who was reportedly the chairman of the group that came up with the recommendations for what would ultimately become the 1976 Devices Amendment, with its three separate classifications for medical devices, with different regulations and regulatory requirements for each.

CM: Well, Dr. Cooper was actually at the NIH, in the Division of Cardiosurgical, for a while, and I think he went from NIH to become the dean of New Mexico or some, one of the universities, I think, and then ultimately became the undersecretary of health and education. He was an M.D.-Ph.D. pharmacologist by training as well, but was a very good friend of the Department of Cardiac Surgery. And I don't know, it's been a long time since I've looked at that report, but one of the other people that was considered to be very, very pivotal in that whole thing was Paul Rogers, who was an attorney in downtown Washington. And I knew Mr. Rogers, and I don't know whether he was in that original committee or not.

SJ: He recently died.

CM: I know he did. I saw that. He was a wonderful man and was very much involved in the whole devices amendment and what have you.

I told you I was on the Circulatory Systems Panel for 10 years, from 1978 to 1988, and I felt compelled to . . .

SJ: That was a panel as an advisory committee?

CM: Mm-hmm.

SJ: And what advisory committee [unclear]?

CM: This was cardiovascular.

SJ: Cardiovascular, right.

CM: It was called the Circulatory Systems . . .

SJ: Panel.

CM: Panel. And I was a member for four years, and then a consultant for two years, and then chairman for four years.

SJ: And that handles heart valves and . . .

CM: Everything.

SJ: What else?

CM: Everything on the cardiac: The original angioplasty balloons, heart valves, stents, pacemaker, pacemaker leads—anything for the cardiovascular system. That was, the medical device would come through that panel.

And, as I told you, midway through the development of the Starr-Edwards ball valve, a change had been made because of the amount of movement of the ball inside of the cage. It really beat up the fabric a lot, to the point that it would then fray, and the patients would develop obstruction of the red blood cells and what have you. So the initial solution to this, back prior to 1976, was, if you had an aortic valve, is to decrease the distance between the edge of the ball and the strut, to decrease it so it wouldn't have as much latitude to go up and down. And, unfortunately, if they got just a little bit of thrombus on the strut, the ball would stick in an open position and the patient would develop wide-open air insufficiency and usually die.

And I had one such patient at NIH, and we found out what was going on with him. And I thought at the time, we should know when changes are being made to the valve. It shouldn't just be from engineering to the bedside. There had to be a process.

I was delighted when the 1976 Devices Act came along. I think it really did a lot to protect the patients' interests and safety.

You know, sometimes you don't have a choice.

I remember one time I was operating on a patient for [unclear] coronary disease who had been attempted to be operated on twice before, and they couldn't find any sap in his veins. They'd been stripped for varicosities. And so I had—and this is prior to the use of the internal mammary artery. So I had hoped to use a Dardic graft, which was an umbilical cord, which is fixing glutaraldehyde that then had fabric graft around it, and it was just too large of a device to use. And I had been working on something in the animal lab where we'd take a vein from the dog and put it on a glass rod and fix it to glutaraldehyde, and they were sitting in a mason jar. And I had no choice but to have someone from the animal lab bring that over to the operating room, to rinse it and use it, because there was no fabric graft like a Dacron graft down at 4 millimeters that works, and we still haven't been able to develop one.

So there were times you did things totally out of . . .

SJ: Did that work?

CM: For a very short time, very short time.

SJ: It thrombosed or . . .

CM: It thrombosed, yes.

I think it's the residual glutaraldehyde that was in it. There's no way we could get it out like they do heart valves and all. There's less than one part per million of glutaraldehyde in solution [inaudible].

So there were some things that happened, I think, at the NIH that contributed.

But I think the large role that NIH played was the development and publication of all the hemodynamic and angiographic data that went along with diagnosis of various types of lesions and congenital lesions and what have you, and then what the results were after that.

Some of the longitudinal studies that were done in people, like by Bob Balaban, that sort of set the standard in terms of, you know, you really want to [unclear] before certain dimensions are exceeded in the left ventricle. And most of the universities and prior practices don't have the luxury in the budget to be able to bring people back repeatedly for repeat echoes or catheterizations and what have you, and I think that was the major impact the NIH had in the early days of cardiac surgery. And, as I say, with the advent of echocardiography, intervascular [unclear], intracardiac echo, these are all, with the exception of the ICE, the intracardiac echo, are all noninvasive. So it's much easier to study patients now, but that wasn't so in the 1970s and up to the mid-1980s.

SJ: Did NIH develop [heart valves], other than the one that Nina Braunwald developed? By the time you came, was NIH developing any valves of their own? Did NIH have any commercially successful valves?

CM: No, no, not to my knowledge.

SJ: So, your contribution really was in the testing and the documentation.

CM: Right.

SJ: Of the effectiveness of ones that were being, becoming commercially available. Okay.

CM: [unclear] Dr. Reese did work with the Hancock Laboratory on the design of one of the original Hancock valves and put the first one in.

And then we were involved in the development of the atomic heart pacemaker, as I mentioned to you yesterday.

SJ: Oh, yeah. Let's talk a little bit about that.

CM: In the early days of pacemakers, going back into the '60s, we used a mercury battery, which had a life expectancy of about 18 months, maybe 24 months if one used it a lot. So we were looking for a power source that would last longer than that, because every time the batteries run out, you'd have to make an incision over the pacemaker and replace it. And we started developing the plutonium-238 pacemaker, which had plutonium-238 in it, which had a half-life of 57 ½ years, and it still had enough energy then, at 57 ½ years, to keep a pacemaker going.

SJ: And what year is this roughly?

CM: That would have been 1968.

We had five prototypes that we developed with the Atomic Energy Commission; we got the source of the plutonium. We did all the animal work at the NIH in terms of testing the durability of the device. And we implanted, I think, three or four of the five that we were licensed to implant in humans. And then the lithium battery came along, which had a much higher life expectancy.

SJ: You said something that triggered something for me. You talked about authorization to implant. Where did the authorization come from in '68? Of course, that was before . . .

CM: The Atomic Energy Commission.

SJ: Ah, thank you, okay. It didn't have anything to do with FDA or you didn't have . . .

CM: No. I mean, they had to keep track of where the plutonium-238 was.

SJ: That's what they were interested in.

CM: And that's what they were interested in.

SJ: Not so much the patient care at that point.

CM: I actually operated on a small girl from Pakistan who had a ventricular septal defect and closing of the septal defect created a heart block. And I didn't want to put a big pacemaker for an adult patient in her, and we had a smaller plutonium pacemaker, which I had to get permission from the AEC to implant because she was going out of the country with it. So it was primarily keeping track of the plutonium-238.

But that, fortunately, was replaced by the lithium battery, which is considerably cheaper, and they don't have the regulatory issue, now through the FDA, but not through the Atomic Energy Commission.

SJ: Were there any other atomic medical devices that they were working on, atomic power?

CM: Well, I think they were considering some for some of the artificial hearts, but I don't know of . . . None of the current ones that are on the market.

SJ: The pacemakers weren't, were they?

CM: No. It came so closely on the heels of the lithium battery development, and usually you can get three to five years out of the lithium battery, so you wouldn't have to have all the hassle of regulation and trying to track these patients throughout the world.

SJ: . . . when the manufacturer was making changes in the valves. Can you talk just a little bit more about that?

CM: When the ball-bearings problem came along, it was primarily with the aortic prosthesis. We had very few cases that were reported with the mitral prosthesis. I don't know why that is.

But then all of a sudden, Edwards Laboratory would come out with the 1200 series valve, and they'd say, "Well, we changed the cure process," but there's no testing about is the new cure process any better than the old cure process, because there was no procedure looking at this.

And then they would go to the metal valve, the ball of the pyrolite, which is a 2300 and 2400, 2410, 2420, and you had some idea because some of it you could see with your eyes. But there really wasn't the testing that went on after 1976, where a lot of the engineering things had to be tested.

SJ: Was that due to concerns about trade secret, confidential . . .

CM: In part, in part.

SJ: You didn't want to let your competitors know what new surfactant or new process you had come up with and were using.

CM: I mean, today we can get the Summary of Safety and Effectiveness on these devices, Class III devices, and you'll have some information there about the testing and so forth, bench testing and toxicology, but we didn't have all the nuances of testing the pre-clinical IDE before 1976 that we do now.

Just one example of how this can affect things: I was operating on a very small woman one time who I could not get anything more than a 25-millimeter Hancock valve, which is the smallest one they make. And I looked at the valve, and what is usually a white sewing ring covering of the stents looked like [unclear] curtains. It was sort of a tea-stained color. And as I started to place the needles through the sewing ring of the valve, the fabric of the sewing ring began to split and fragment, exposing the sponge rubber below it. And so I had all these sutures in, and I had all this exposed rubber, and I didn't have another 25-millimeter valve.

SJ: Not good.

CM: Not good. So I actually cut a doughnut from the pericardium out and threaded the needles through the pericardium, put that down, the needles through and put that down over the exposed rubber.

SJ: On top of it.

CM: And then I tied the sutures on top of that to cover up the exposed rubber. That's one of the things that I call, you know, it's the mother of invention by necessity. And so I knew there was . . .

SJ: That must have taken forever.

CM: No, it didn't take that long.

SJ: Okay.

CM: But I called the manufacturer, I think. Medtronic had bought Hancock Laboratories' valve. And I called them and said, "I need to know something about the valve that I put in." I said, "The sewing ring didn't look correct, and it fractured when I put the needles through."

And the person I was talking to said, "Well, you must have been using a cutting needle rather than a tapered needle." I said, "This is not my first valve I've put in." I said, "I don't think my scrub nurse would give me a cutting needle and know I wasn't using a cutting needle." And it was during the time . . .Anyways, he said, "I'll have the head of the department call you back tomorrow." So this fellow called me back and he said, "I understand you had something that looked like a tea-stained valve and that the fibers fractured." And I said, "Yes." He said, "Well, you must have used a cutting needle." I said, "I didn't use a cutting needle." And he said, "Well, how did you get it out?" and I told him. He said, "What's your name again?" I said, "McIntosh." He said, "You're not the chairman of the Circulatory Systems Panel, are you?" And I said, "Yes." What I found out at that time was it was not required. That valve had gone back to the company three times to be fixed again with glutaraldehyde because it wasn't used; the 25 millimeters that people hadn't used. So that valve probably had been on the shelf for eight to 10 years by the time I used it. And I went back to the agency at that time and I said, "You know, there really should be a date of manufacturing. If the valve is reprocessed, we should know that in the field," because, clearly, it was brittle because of all the glutaraldehyde that had been used. So that was another example of why I think it's important that the FDA be able to not only monitor the process of clinical trials and product development, but also post-market surveillance. That's particularly true now, I think, with endovascular therapy because durability is a major question because these grafts are being put in by minimal-invasive procedures, and we know how long graft material lasts with an open operation for a valve. So, I think we've got some standards at least we can compare it to.

SJ: Excellent.

NOTE: As I was walking Dr. McIntosh out, he told me that there was a Life Magazine issued sometime between 1960 and '62, when the Clinical Center operating room was opened up, and they took pictures from the atrium and from the dome of the new surgery, so I need to look for that. Secondly, he was saying that they had, in the early operations, they had in the operating room audiotape, and they taped every operation. And he said when they went back and listened to the tapes, that every other word—they couldn't really use them very well because every other word was a swear word, which he said was an indication of how many things used to go wrong in surgery. Every time you went in to do something, something seemed to go wrong. So it's a commentary on the fragility of some of the early surgical techniques and surgical equipment.

END OF INTERVIEW