INTERVIEWEE: Dr. Robert Califf
INTERVIEWER: Jessica Roseberry
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CALIFF INTERVIEW NO. 1

JESSICA ROSEBERRY: This is Jessica Roseberry. I'm here with Dr. Robert Califf. He is vice chancellor for clinical research and director of the [Duke] Translational Medicine Institute. Today is June 11, 2007 and we're here in his office in the North Pavilion. And I want to thank you, Sir, for agreeing to be interviewed today. It's a privilege to talk with you.

ROBERT CALIFF: Glad to be here.

ROSEBERRY: If it's all right with you if you don't mind giving me a little background of yours and how you got into the field of cardiology, if that's okay.

CALIFF: Well, I originally came to Duke in 1969 as an undergrad, and I was going to be a clinical psychologist until I worked in the state prison system in South Carolina for two summers, my home state. And thought, Well, gee, I'd like to do something that's a little more tangible. This looks—this is worthy work; but I didn't find myself to be very successful at changing criminals into useful citizens in short periods of time. And I think that sort of pushed me over to something that was very tangible, which cardiology really is. And in fact after graduating from undergraduate school, since I decided to try to become a physician late in undergraduate career, I worked as an orderly in a hospital in Greensboro where my wife was finishing nursing school. And I remember walking into the emergency room almost on the first day and seeing a patient defibrillated, and there

you're taking someone who's dead and bringing them back to life. That's about as tangible as you could get, so that pretty much clenched it at that point that I decided cardiology would be a good field.

ROSEBERRY: That sounds very exciting.

CALIFF: It really was. If you think about the time when I came along, really just prior to that the concept of defibrillation had come in, so the understanding that the heart is an electrical and mechanical organ that controls so much of life and death and function and that it can be controlled was a new thing. So it was really a great time to come along in cardiology.

ROSEBERRY: So what else was going on in the field during that time?

CALIFF: Well, you know, eventually I'd applied to a number of medical schools. I didn't think I'd ever come back to Duke after finishing as an undergrad. It was a very tumultuous time, '69 to '73. We spent a lot of time not going to classes and getting tear gassed in Washington and other things at the sort of height of unrest over where the country was headed. But I got into several medical schools including Duke, and in the end it seemed like the best option for me, so I came back. And I still distinctly remember the now late Fred Cobb giving a lecture to the second-year medical school students where he said that heart attacks are not caused by blood clot. And the theory at the time was that there was a mismatch of supply of blood of oxygen to the heart and the demand and that thrombus or blood clot in the artery wasn't the culprit. And of course very shortly after that, as I started my fellowship, we were able to do acute angiograms in people with heart attacks and see that, in fact, it was blood clot after all. The problem had been that before the studies had been autopsy studies, and when you die the blood clots lyse and

they're not there when the pathologist looks at them, and so this was a revolutionary change in the field of cardiology. But the biggest insight for me was as a medical student I needed a job to make some extra money to pay the bills. And I ended up getting a job working collecting information about patients that go into the cardiology databank, which had started up at that point, and it seemed very clear to me that computers were actually going to be valuable. Now, that sounds very simple today, but in the mid 1970s, remember that computing was something where you punched holes in cards and stuck them in this huge machine that took up a room and it could sort of sort things, but the kind of things that we take for granted today just weren't possible. But there were visionaries at Duke at the time who really saw things that other people couldn't see.

ROSEBERRY: So what was your job at the databank?

CALIFF: I was actually working in the clinic just working up patients and filling out forms, and it was a job. It wasn't anything highly intellectual, but it helped pay the bills in medical school.

ROSEBERRY: So did that begin to turn your head toward the field that you would eventually choose?

CALIFF: Well, it turned out, you know, Duke has had this unusual curriculum for medical schools where the third year is available to do research, and the pattern has been that students have been encouraged to do basic science research. But I was very attracted to clinical research because of the experiences that I had had, so I signed up to work with the cardiology databank for my third year of medical school. And I signed up for a—what I thought at the time was a really interesting project. They had been funded to put Holter monitors on patients with documented coronary disease, and the theory was that

by measuring the heart arrhythmias you could predict who would have sudden death. Now, going back then and even today, sudden death is leading cause of death in developed countries; people dropping over dead is not an unknown thing, and it tends to happen to people at the prime of life. It's a big concern, and it was pretty mysterious. So I signed up to work on this research project with Jim Margolis who was a young investigator, and I walked into his office the very first day of the third year of medical school, and there in his office were a bunch of boxes. He was packing up to leave and going to Miami because of a practice opportunity there and leaving academic medicine. But he said, "Don't worry, Galen Wagner will take care of you." So that was when I met Galen, and he helped me get through the third year of medical school, and I learned a lot in that year.

ROSEBERRY: So did you continue with that sudden death research? Was that—?

CALIFF: I did.

ROSEBERRY: The same thing?

CALIFF: I personally put Holter monitors on hundreds of patients, and we analyzed the tapes, and I worked with the cardiology fellows. It was a great experience. I sat near Kerry Lee, who was the original biostatistician on the Duke campus, and it was quite surprising what we found as the data came in. Sure enough, people had had these heart arrhythmias. So you and I are walking around, we'll occasionally have an extra heartbeat. People who have blocked up arteries will have often many extra heartbeats or even prolonged runs of extra beats: so-called ventricular tachycardia. And sure enough, as predicted, these arrhythmias, if you have them, you're higher risk for dropping over dead suddenly. But what was more interesting was the function of the heart was a much

stronger predictor. So we wrote a couple of papers that said the arrhythmias are interesting but that's not the big issue. It's the ability of the heart to contract that's the key issue. And we predicted that treatments needed to be named at preventing sudden death in people with heart dysfunction more then people with ambient cardiac arrhythmias. And my internship year out in San Francisco I had my way paid to come back and present that data at the American Heart [Association] meetings, and people thought we were just completely wrong. It turns out now, twenty-five years later of course that the indication for putting in a cardiac defibrillator is heart dysfunction not arrhythmias. So Dr. Lee with his very cool analysis of data, getting surprising answers really taught me a lot.

ROSEBERRY: So obviously you utilized the databank for that project.

CALIFF: That's correct. So the fact that we were one of the first places to be collecting what now would be called phenotypic information, we just called it clinical characteristics. You know, Who were the patients that we're seeing that are being seen in the clinic and going to the cath lab? enabled us to do analysis that other people couldn't do and to see things using sophisticated biostatistical methods that other people weren't able to do.

ROSEBERRY: So did you, I know that you eventually moved into the CCU [coronary care unit]. Is that correct? Is that—?

CALIFF: Yeah, so during that third year I also spent a fair amount of time with Dr. Stead, who was the person that really had the insight to make this happen and put the databank together really in terms of the conceptual basis. And worked closely with Bob Rosati who was really leading the effort at the time. And of course David Pryor was a

year ahead of me, and so it was a really fertile time for thinking. Back in those days in clinical medicine, you would work five or six hours a day on the clinical scene and then you'd have time to actually talk and think and write. These days it's a very different pace on the clinical scene and much more difficult to actually be intellectual. So Phil Harris was also there at the time. He had come from Australia to do his research time, and he was one of the more creative people I had met, and then Frank Harrell, who is now the head of Biostatistics at Vanderbilt and probably the best biostatistician in the country at visualizing data. And I probably learned more from Frank than anyone about how to look at data and actually see the patterns in the data. Kerry is just as solid as you get in analyzing data. Frank is more a wild, creative sort of a person. So from that I really was hooked by the time I had finished. And I think the sentinel moment for me was when Dr. Stead asked me to come to a cath conference, and he showed me what had happened with the last hundred patients like the patient that was going to be discussed. And they'd done better with surgery than with medical treatment, but the last several patients that had been operated on had died at surgery. So he said, "Go to this conference, and you watch them; they'll say surgery's a bad idea for this next patient because of their most recent experiences. The human brain is not really capable of aggregating all this information. Only a computer can do it. So they're going to make the wrong decision based on the way doctors think." And he hit the nail on the head. He was exactly right. They made the wrong decision. It wasn't their fault. That was all; that was the way people thought at the time. And interestingly there's a book that's a bestseller now called, I think its *How Doctors Think* by Jerome Groopman. You could take what Dr. Stead said in 1976 and it would be identical to what Groopman is doing a bestseller on today. So I was

hooked on this, and I went out to San Francisco to do my internship and residency. And for better or worse my wife, who is a South Carolinian, too, was not excited about going to San Francisco. We were just having our first child right before the move, and she made me line up a fellowship before I left as a condition for going. So I was already signed up for my cardiology fellowship at Duke before I left, and of course after we were out there a couple of years, she didn't want to come back. But we came back, and I started my fellowship back here working in clinical medicine but also doing research with the databank.

ROSEBERRY: Can you tell me about Dr. [Robert] Rosati?

CALIFF: Yeah, Dr. Rosati was a very inspirational character who I would characterize as a complicated person. He's still here working with the rice diet [Rice Diet Program] now, and he was the kind of person that would always challenge authority, something that I personally appreciate. And he would question people, and he was willing to go against the grain. But I also understand based on my own experience that that can wear thin, and I think it was very tough for him to be leading an effort that with Dr. [Eugene] Stead now no longer charge at the institution was not necessarily highly regarded by the more traditional thinkers. It was really a counterculture effort. And so Dr. Rosati was very helpful to me, and I personally owe him a lot, and I think David Pryor would probably say the same thing. I know you're interviewing David as part of this historical effort. But when I came back for fellowship, it was clear that Dr. Rosati was kind of worn out, and just as I finished fellowship he announced that he was giving it up, because he couldn't really see that it was going to be kept financially viable. That was pretty

devastating in a way, but I was already a convert by that time and probably not smart enough to realize that it was going to be an uphill struggle to keep the databank alive.

ROSEBERRY: So in what ways was he challenging authority while he was running the databank?

CALIFF: Well, at the time there was a view that Duke doctors had that they were somehow magically imbued with this talent to be able to know exactly what to do with patients. And he could obviously see that many times they had no earthly idea what they were doing, and so he would bring these issues up, and it was often not well received. Remember this is back in the days of the more hierarchal, paternalistic medical model. That's the way it was. People came to the doctor from—particularly Duke in the South was a very well-known institution. There weren't that many well developed academic medical centers at the time, so people would come from all over to see a famous Duke doctor. And here was Dr. Rosati saying these guys actually don't know all that well what they're doing, and I can show you with a computer. Well, that didn't necessarily make friends. And I'm actually still unclear of a nice way to say that. Because you're really challenging someone's personal view of the world that's been built up over the course of many years. He was also wonderful at raising conceptual research issues that we had endless arguments about. That was fun, though; that wasn't a problem for anyone. An outsider might view it as rugged and difficult, but I think when you're having intellectual arguments its fun, and it was a great thing to do. We would have Friday afternoon meetings at the pizza parlor with beer and go at it like academics are supposed to do. These days people are working in the cath lab until six or seven at night even on Friday, so these kinds of things have gone by the wayside.

ROSEBERRY: What were some of those discussions about?

CALIFF: A lot of discussion about observational treatment comparisons, which is a topic people still don't understand very well, but it's coming into it's own right now. And in fact I was asked to be a major participant in an Institute of Medicine meeting just a few months ago. Because people are, things have sort of gone cycle—and I'm sure we'll discuss it further as the databank evolved—but randomized clinical trials have become the gold standard for accessing whether a treatment is beneficial compared to other treatments. But it's still the case we can't do a randomized trial on everything so the question is, Can you use observational information to make valid inferences about the best treatment? It is very complicated, but I have to say the arguments we had then prepared me very well for the next really twenty-five years of work in this area. We were hitting all of the relevant topics even back then.

ROSEBERRY: So that argument is not necessarily resolved in regards to observational—?

CALIFF: No; I think what almost everyone agrees on is that when you can do a randomized trial, it's the most valid. We need to use other data to make decisions, because we can't wait on the final answer. People need to be treated and diagnosed, and the argument is all about how far you can go in that regard, where you can feel comfortable and where you can't, and that's very far from resolved.

ROSEBERRY: So were there different people who had different viewpoints on that, obviously?

CALIFF: Well, we—at the time we were actually sort of poster children for observational treatment analysis. And I remember distinctly—and I sort of had a

flashback about this last week. I was at the National Heart, Lung and Blood Institute [NHLBI] board of external advisors, which occurred in Building 31 at the NIH [National Institutes of Health]. Which anyone whose done cardiovascular work knows that building. It's the headquarters for the NHLBI, and we used to get shuttled up there to be harangued by the randomized clinical trials expert for daring to do these observational treatment comparisons. The Cox model, which is a key tool for that kind of work, had really just been developed. Kerry and Frank were two of the first people to really apply it. I was able to sit down at a computer as a third-year, fourth-year medical student and produce predictions for patients about what was likely to happen if they were treated medically or surgically. That was twenty years ahead of its time. So we learned a lot and we had ideas, but it's still a work in progress.

ROSEBERRY: Well, what are some of the key things that stand out in your mind as you kind of reflect on that particular time in the databank's history and in your own history as well?

CALIFF: Well, the key things for me are that, I mean, first of all the lesson that people who really make a difference often are seeing things that other people just can't see. And the line between being a visionary and being an outcast is a very difficult line to walk. And I'm sure Dr. Stead had many days—. Because remember part of his history is that he retired from being chairman of Medicine at a young age and devoted a lot of his energies over the next ten or twelve years to trying to make this dream of computers in medicine happen. I'm sure he had many days when he thought, I can't believe these people don't get it. But knowing when to speak out and when to push the buttons and when to hold back is very complicated. So that was number one. Number two is it was

just fun. And I think many of us long for the older days of academics when you really had time that was built into the expectation to just have intellectual discussions and arguments. And anything we can do to recapture more of that will be, I think, a very useful thing. But those are probably the main things.

ROSEBERRY: Now, when you assumed leadership of the databank, was there that same feeling of walking the line between being an outcast and being a visionary? Was that still in place, that—?

CALIFF: That was more fear, (*laughter*) and I know you've talked with David Pryor, so it would be very interesting to compare our recollections of what happened. But David was a year ahead of me, and I was just finishing the fellowship when Joe Greenfield had just been made chief of Cardiology. Joe is and was an unusual person. And I still distinctly remember he called me into his office and said Eric Conn, who had been running the CCU for only a year, had announced that he was going into private practice in Chattanooga and that they needed someone to run the CCU, and he thought I should do it. And I said, "But Joe, you know, I've only done two years of fellowship. I'm not even board eligible." And he said, "We'll take care of that." And I essentially did a hybrid year where I ran the CCU and also finished my fellowship. And that was ongoing, and then Rosati said, Well, you know, I'm giving this up. So Joe had David and I in, and he said—essentially what he said was, "This thing's losing a large amount of money." I think he said five hundred thousand dollars a year. "I don't think it's worth anything, but I'll give you guys five years to figure it out." That's vaguely my probably altered recollection of what happened. And we sort of looked at each other and said, Is this something we want to stake our careers on? We knew that as cardiologist we could go

into practice and do a lot of good and make money at the same. Not a bad thing to do. Joe at the time was offering me the princely salary of thirty-five thousand dollars a year to be on call every weeknight and every other weekend, covering both the Duke CCU and at the time the Durham County CCU. So it was essentially a life of living in the hospital. So David and I went away and came up with a plan for how to resuscitate the databank. And specifically Rosati's concern was that bypass surgery had been sort of what the databank had been studying, and it had sort of come into its own, and what was the future? What he didn't know was that angioplasty was about to hit the scene, and of course, we didn't know that either, but we came out with a diversification plan that included getting paid adequately for producing computerized reports. Remember in 1982 the concept of producing a report by a computer was still a new thing; hard to believe in 2007 that could be the case. It also included collecting money from insurance companies for actuarial predictions. We were one of the few groups that could actually take a person with heart disease and produce a projected life expectancy, which is critical for insurance. It included at the beginning to do clinical trials, which was very counterculture at Duke, because since Duke doctors knew everything, there was never a reason to do a clinical trial, since your doctor knew exactly what ought to be done to begin with. And we had a few other things here and there that we were going to do. That was probably the most creative point in my career, because we were scared to death. And David and I spent a lot of intensive time together coming up with a plan. It also included dividing up the responsibilities where David essentially ran the databank, and my job was to run the CCU and keep the clinical enterprise from becoming completely dissociated. Because one of our concerns was that if you believed as a doctor you knew the answers already, why did

you need to be supporting this computer stuff? And we needed to keep it more as an integrated whole.

ROSEBERRY: Do you feel that Dr. Greenfield maybe didn't—you mentioned that he said it maybe was worth anything, do you feel like he supported the work of the databank?

(*sound of beeper going off*)

CALIFF*:* Sorry. I think Dr. Greenfield's strategy with people was to provoke them into doing things that he thought they ought to do. And he was the master at making people feel supported. And it's an unusual talent to make people feel they're so supported when he gave you so little in the way of actual support. And he had a number of psychological ploys he would use. So his desk was the oldest desk he could possibly have. So there you go to see your boss, and he's got this pitiful old desk and no fancy things in his office, and you would feel guilty about asking for anything. And that, of course, stimulated you to go out and figure out how to do it yourself. In many ways it was a good thing. So I would say that David and I both felt very supported by Joe Greenfield in those early days. If there was a fault it was we weren't smart enough to know what to ask for. And it might be fair to say he took advantage of that, but we ended up with great careers because of it, so who knows in the end, maybe it was a fair trade.

ROSEBERRY: Well, how did you come up with those avenues of tapping resources? What was there; were there some of those in place and kind of—?

CALIFF: Well, the starting of all that, I mean, all that had been started. David had really worked very hard over the course of his fellowship and later to really push the frontiers of what could be done with computers. And Ed Hammond was developing his effort at that

point. They realized that the computer system they had for collecting and aggregating the data was rapidly becoming outmoded. And Ed really had come up with this new approach called TMR, The Medical Record. And I wouldn't say that David and Ed always got along well together, but they shared a vision of generally what should be done. And in fact many of the issues that they struggled with are still playing themselves out in terms of electronic health records and how they actually work today. So amazingly at that time I think David really had the insight into where quality in medicine and electronic health records were going. Ed had the vision for how computers were going to work. And in fact, today Ed is still on campus, and he is one of the godfathers of medical informatics and went on to do things that really have linked together computing and medicine all over the world. I mean, if you ask people who are experts in computing and medicine, Ed would be in the top five or six people in terms of what he's accomplished. Both interestingly were not necessarily well received in their own environments because they were saying things that were way ahead of their time.

ROSEBERRY: Is that true for you as well with the clinical trials?

CALIFF: Well, what happened with me was that because I had control of a domain that was critical to the institution and Joe supported it, I had a link to the clinical operations which kept me sort of grounded in the institution. So did our clinicians like the idea of doing clinical trials? No. But I started out with clinical trials in acute myocardial infarction. Remember right as I started fellowship as I said we were able for the first time to do angiograms and see that coronary arteries getting completely occluded by a blood clot was what caused heart attacks. And we started experimenting with drugs that could lyse the blood clots, and this was revolutionary, and a lot of clinical trials needed to

be done to sort that out. So it also turned out that some of my professors at UCSF [University of California, San Francisco] had started this new biotech company, Genentech, in San Francisco. And some of my fellow house staff officers were now distributed across the country as leading cardiologists, and we developed a little network to do clinical trials. What we did was to leverage the computing capability of the databank with the fact that we were running very cutting-edge clinical practices around the country. And we said, Let's put those two things together and start figuring out how to really take care of heart attacks. Now, the NIH at the time had started doing this in a group they called the TIMI group, thrombolysis and myocardial infarction group, run by Eugene Braunwald, one of the godfathers of cardiology even back then. And I still work closely with Dr. Braunwald today doing clinical trials. He's got a few years on me, but he works as many hours as I do and loves it. But we thought, We're just a bunch of young folks who are just finishing fellowship, so we'll call ourselves the TAMI [thrombolysis and myocardial infarction] group to make fun of the more established TIMI group. And this was the beginning of a really wonderful period in my career where we used the talents in the databank and did clinical trials at a very low cost that would be considered highly experimental. I mean, literally to the point where we would get on an airplane and meet in a place and just look the films of the cases that we were doing, because the things we were seeing had never been seen before. This is a small group of five or six young leaders, and we're still all good friends today. We've been through many ups and downs in our careers but still keep in touch. This made money. It didn't make a lot of money, but because the most exciting research was really studying new therapies that were being developed by industry, industry pays for its research, and this

really built a little enterprise that we had that was almost pure fun and very highly connected and a precursor to research networks that have developed since that time.

ROSEBERRY: I know that Dr. Synderman had just come from Genentech, or was at that time, or—?

CALIFF: It was kind of interesting. As this was evolving, Dr. Synderman was the chief of Rheumatology at Duke and had a laboratory here, and I remember seeing him; he was always jogging, I was playing tennis. And he got recruited to Genentech under the pretenses that his immunologic capability would be very highly valued because this new drug to lyse blood clots called tPA [tissue plasminogen activator] that they had developed was about to get on the market. So Ralph arrives in South San Francisco. He's all set up to develop their new immunologic drugs largely based on the profits they were going to make from the sale of this new thrombolotic agent, tPA. And the FDA hearing occurred, and it was a debacle. They got—did not get approved, and he had to spend his next year trying to get tPA approved, and that's how I really got to working with Ralph, because we were experts in the topic and spent a lot of time discussing the strategy of what to do with tPA. And so eventually it did get approved. He did a few more years of research at Genentech really developing new drugs, and of course now Genentech is not a cardiology company at all. It's mostly an oncology company based largely on the molecular biology that was developed at that time leading to a whole bunch of new targets that they've subsequently taken advantage of. And Ralph was recruited back to Duke by Joe Greenfield really predominantly leading the charge that he would be a great chancellor for health affairs to follow onto Bill Anlyan.

ROSEBERRY: And you were using, you were testing tPA against streptokinase. Did I say that correctly?

CALIFF: Well, originally in the TAMI trials, which actually I think ended up being eight different trials, we were really using tPA as a base and then we were trying to understand what the care of the patients ought to be. So our very first trial was looking at whether you should do an angioplasty right after you gave the drug. So this is really exciting. I would—they would page me. I'd go jump on the helicopter. We'd land in a little town. Give the tPA. You know, the fire engines would meet us at the local hospital when we landed, and we'd put people on the helicopter and bring them back in and then randomly either do an angioplasty or not at that time. Very new stuff, really exciting. I still have one patient who I personally defibrillated on the helicopter who's still alive today, and I'm seeing him in clinic. So those were more How do you treat the patient? rather then evaluating the drug. But as that was going on in Europe, they were hatching the concept of the mega-trial, and the concept of the mega-trial is that since most of what we do therapeutically actually has a pretty small effect on how people do medically. You need thousands of patients typically to really find out what a treatment does, and of course they were completely right. If you're, in 2007 if you just follow the Avandia case, it's pretty clear that we've been off base in accessing therapeutics for a long time. And the Europeans did a couple of mega-trials that seem to imply that tPA was not better then streptokinase. And that was real bad news for Genentech because tPA was being sold at two thousand bucks a head, and streptokinase was about four hundred and fifty bucks a head. So if you had two drugs that got you the same result, you'd obviously use the cheaper drug. So because of our friendship that we had developed with Genentech over

the years, not evaluating tPA but more evaluating ancillary treatments: How much Heparin do you give? Should you do an angioplasty? Should you give combinations of drugs together? they came to us and said, We've got to do a competing mega-trial that's based in the US. Because the concern was that maybe the Europeans were not giving it the best possible way. And Genentech at the time was under congressional investigation for some things that they had done, like companies sometimes do. So they said, If you agree to do this, we'll hand over the money, and you can design and run the trial on your own. At that point the largest trial we had done was four hundred and fifty patients. And we did the sample size calculations and came out with thirty thousand. So this was a somewhat frightening concept, but we didn't know any better, so we said, Yeah, let's do it. So there was very serious institutional discussions that occurred at the time. Obviously Dr. Synderman had a conflict of interest. He had just come from Genentech. There was a bit of risk about bad publicly if Genentech got into more trouble. There were financial risks. What if we messed it up? And this was—the budget for this trial would be in the tens of millions of dollars. But one of the reasons I've stayed at Duke all these years is every time it comes to a hard decision, or almost every time, in my view, the supportive decision got made. So in this case we got it all worked out and did the GUSTO I [Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries] trial, which indeed was comparing tPA and streptokinase. But to randomize thirty thousand patients—and it eventually turned out to be forty thousand, because after we had enrolled the first thousand or so our European friends declared that the streptokinase regimen we had needed to have Heparin given with it and—or needed to not have Heparin given with it and declared a public health alert about

this issue—we had to add an additional arm with ten thousand more patients. So to pull this off we had to build a very extensive infrastructure, which became a key component of the overall effort.

ROSEBERRY: So was this now the DCRI, or was it still—?

CALIFF: No, it was really at that point a component of the Department of Medicine and the Division of Cardiology, and it just grew. We moved off campus to a set of buildings that included the old Erwin Square building and several buildings out in north Durham, and we were just growing and growing as we did more clinical trials. Things that I had no understanding of were going on in the meanwhile between Joe Greenfield and Ralph Synderman that I guess were not necessarily pretty. There were major disagreements, and I think partly because of that our finances were never completely shared around the institution, we were allowed to grow. It's likely, I think, that if we had been more visible to everybody on campus, we probably would have been stifled by bureaucracy, but we weren't. We kept growing. It was a very exciting phase of rapid growth, a lot of late nights, concern, learning new things about how clinical trials were done, testing new treatments that were very high risk but high yield that have ended up saving many lives. One anecdote that I find particularly gratifying now is two of our collaborators were Eric Topol and Bill O'Neill. They were both at the University of Michigan, and Eric was more of an advocate of the use of tPA. Bill was more of an advocate of the use of angioplasty as primary treatment for heart attack. So here we are with the leading cause of death in the developed world, heart attack, often manifested as sudden death—which we've already discussed—and we have two competing treatments. Well, tPA was winning the day. After GUSTO I, tPA was the winner. Well, Bill O'Neal called me and

said, “I still think angioplasty is better, but I can’t get anybody to fund the study that needs to be done,” and he said, “Would you be willing to at least run a registry of primary angioplasty?” And we said, Yeah, I think that’s worth doing. We did that. The so-called Primary Angioplasty Registry.

ROSEBERRY: I’m sorry. What does it mean to run a registry?

CALIFF: That means rather then randomizing people, you just say you have a group of doctors that are going to treat a bunch of people a certain way, and you just collect the information about them. Think of it as a databank but involving multiple hospitals. And we put that together and did it, and the results were spectacular. And that ultimately led to bringing things back together in the GUSTO II trial where we randomized to tPA or primary angioplasty. And primary angioplasty really over time has evolved as the winner. tPA ended up being the loser. So tPA had its day in the sun. It was beneficial compared to striptokinase. But if not for sort of having the leeway to do things that were sort of independent of things like peer review funding—but you had the freedom because of the money we had from the GUSTO trial to do some experimental things. Primary angioplasty might not have seen its day, at least not as soon as it did.

ROSEBERRY: What tools that were born in the early days of the databank were now being able to be used by these—?

CALIFF: Well, as amazing as it may sound now just having computers that could collect data (*chuckles*) was unheard of at the time, particularly at multiple centers. It was a very unusual thing to be able to put this together and collecting data in multinational basis. We actually created systems by taking the skill of understanding how to collect data items in clinical practice and merging that with all of the thoughts from the international

community to develop new constructs for how to do clinical trials that are still used today. An example would be Just-in-Time pharmacy distribution. If you think about it, if you're having to study ten or twenty thousand people with a very expensive new drug, you don't want to end up with a big inventory in every hospital or every practice, because it's very expensive. You multiply a thousand dollars times twenty thousand, and you begin to come up with very large numbers for the excess costs. So the development of Just-in-Time pharmacy was something that we did because we had to do it to make the system work. It was those computing skills that were really critical.

ROSEBERRY: And then on the flipside what's kind of the difference between observational use of the databank and the clinical trials?

CALIFF: Well, I mean, the way I think of it, we—the databank is really a practice improvement tool for an institution and should be a practice improvement tool for individual doctors. And finally we're about to recapture where we were in 1977 really in my view. It's taken us a long time to get back to it, but everyone now in health policy circles is talking about the electronic health record as a critical instrument to have better patient care. So the databank was really a visionary effort to understand how you capture information about patients, keep it on a computer, measure things longitudinally and then use that information for better clinical practice. The randomized clinical trial is a method for deciding what the right treatment is. So the databank is not fundamentally a tool to decide the right treatment. It's a tool to measure what you're doing to help yourself do the right thing more often. The trial gives you the information about what the right thing to do actually is, and what's evolved that's come between the two is the multi-center registry. And that has really taken off now, led by Eric Peterson actually. So that what

we really see evolving now is the concept of multiple practices collecting the same information over time, using that as a group quality improvement tool with very focused efforts by individual doctors using electronic health records.

ROSEBERRY: What are some of those centers?

CALIFF: Well, right now if you look at last week's *Journal of the American Medical Association*, you'll see Dr. Peterson and colleagues' article about the CRUSADE registry—which is not some of those centers, it's almost every hospital in North America—is collecting registry data about its patients with heart attacks. So five hundred hospitals. And it's part of accreditation now to be a hospital to do well by the quality performance metrics that are used in that registry. So I would say it's become globalized and just become a part of standard practice now in cardiology to do things that were initially conceived by Dr. Stead, Dr. Wagner and Dr. Rosati with the help of their computer experts.

ROSEBERRY: Do you feel that the databank influenced the trend now, or is it just—?

CALIFF: Yeah, the databank is like the core place where the ideas and concepts are developed, and by having our own system we can play around and learn how to do things better, ideas are generated from that, and it leads to people thinking differently around the world.

ROSEBERRY: So they might say, Oh, look at Duke, and Duke is doing this well, and so this is kind of what we need to be doing as well?

CALIFF: Or our leaders might say, Here's a way you can do it. And now that there's so many other people doing the same thing, it's not that we're particularly unique, but the history gives us a view that very few other people have. It just came out last year in the

discussions about Clopidogrel and drug eluting coronary stents, which was is a very hot international issue, but the fact that we had not only the data about our patients getting stents and what kind of stents they got, but we also had the follow-up information for years including the medications they were taking, gave us the ability to write a key paper in *JAMA* of the influence the field to a great extent and change the way the recommendations are now about what to do if you have a coronary stint. And six million people around the world with drug eluting stints, so that's nice to be able to have that kind of impact.

ROSEBERRY: Well, how did the databank go from being the databank to being DCRI?

CALIFF: Well, as we evolved in this environment, the GUSTO trial, the growth into hundreds of people and four or five buildings in Durham, and Joe and—Greenfield and Ralph Synderman not agreeing, changes were made in the institution, and there was a decision made to appoint a new chairman of Medicine, Bart [Barton] Haynes. At that point, we were sort of at a place where we had become a fairly significant financial juggernaut I guess you would say. And I was personally being recruited by two places, the State of California—the Bay Area where I'd done my house staff training was really heating up with biotechnology, and there was a view that by combining the universities, the university medical centers that the State of California ran, UCSF, UCLA, UC Davis, et cetera, putting it together with the biotech industry in the Bay Area, then something really exciting could be put together. And then my home state of South Carolina where the governor, David Beasley, was a closet Internet freak who before most people were using the Internet was up late at night evaluating biotech and other technology trends, and the State of South Carolina was recruiting us back. Actually offering that our top seventy

people could move free of charge to the Medical University of South Carolina, paid for by the state economic development commission. So it was an interesting time for me, because I was being recruited by economic development groups for the state governments not by the academic medical centers primarily. The end result of all these changes was that the university asked McKinsey to come in, the famous consultants, McKinsey, in to access the situation as to whether creating something different here would be enough to make it attractive to stay here as opposed to going elsewhere. And sort of like the time when David Pryor and I sort of by ourselves came up with a plan, this was a very interesting time where we sort of envisioned the future. These highly paid young consultants from McKinsey came in. Their job is to force you to think about the future, and we came up with a plan for the DCRI. And the university agreed they thought it was the right thing to do, and we were off and running with a charge to develop what we had done with cardiology for the rest of the institution. And that was the beginning of the DCRI.

ROSEBERRY: So when it was a financial juggernaut it was still within, money was still staying within the—?

CALIFF: The Department of Medicine.

ROSEBERRY: And so then it—

CALIFF: Don't ask me how money got moved around within the Department of Medicine. (*laughs*). I'll let other people describe that.

ROSEBERRY: Okay.

CALIFF: But let's just say that when you do a successful mega-trial, it makes money if it's industry funded. And that money can be used to offset academic costs for things that

you'd like to do that industry's not interested in, and that was a fundamental scheme that we played out. And of course the more academic things you do, the more money you lose, so there's a balance there that has to be kept.

ROSEBERRY: And then when you developed this new scheme of working it became, the money channeled through the institution? Is that—?

CALIFF: Well, the plan from McKinsey I thought was ingenious, and it's a precursor to things that are happening all over academic medicine today. What they said was in order to be an institutional entity, you should report to the chancellor, so I reported to Ralph; but you need to have a board, much like a corporation. The board should be made up of the key stakeholders and those are mostly the department chairs but also all the various CFOs: the CFO of the medical school, the CFO of what then was a precursor to the health system really. It was Duke Hospital at the time. And you should meet quarterly and present your plans in a very transparent fashion, including your financial statements. Well, that was unheard of. Prior to that time this was a very Byzantine organization where people kept things secret—and it all worked out because it was sort of a time when academic medical centers sort of made up their budgets by figuring out what it had cost the year before and then adding some factor, and it would get paid for, but that was just coming to an end. So the McKinsey plan I thought was ingenious, and I learned right away I actually like transparency in reporting what I'm doing to a board, and there were many interesting discussions that occurred about the direction that we were going.

ROSEBERRY: And I'll ask again kind of as you look book on that time what stands out in your mind in what might need to be remembered?

CALIFF: Well, the main thing that stands out is the hard work by a lot of people internally. You know, there's a lot written about organizations that grow fast and how stressful it is for people. This was not an organization for your average person who wanted a nine-to-five type job. It was a very stressful time. We were doing new things. We were turning back frontiers. Our ideas were not always warmly received by people we thought should warmly receive them. So the worker bees, the people who had to make the operations run were often caught in the middle of things and I think made a lot of sacrifices to make this happen, so that's an important thing to remember. Also the support of the institution and the willingness to take risks, and I think one of the things I worry about in the big academic institutions these days is that they've gotten so wealthy and they're doing so well that the boards tend to be very risk adverse. And of course if you're not taking risks you're probably not, in my view, you're not fulfilling your societal mission. So that was a time when people were willing to take risks. And they did it, and it was not unplanned; it was not haphazard, but we were doing something that no one else was doing. And a lot of people said it wouldn't work, but it looks like it probably did. On a sadder note, we're here talking about the databank, I would say that because of the focus on clinical trials and the national and international reputation and other things that were happening in the institution at the time, the cardiology databank fell into great disrepair. And in fact the hospital and the Department of Medicine weren't interested in paying for it. So one of the things that happened that in retrospect is kind of interesting: for a while we were doing well enough financially that we did still get money from the hospital to pay for the reports, but there was always a deficit, and for a while we just paid for it out of the margins that we were making on industry-funded clinical trials

in the DCRI. But then it sort of got to the point where year to year we had other academic priorities. Some years we lost money and there were real questions about Should we just let this thing go? because people in the clinical side of things weren't very interested in it really. It was sort of there, but they didn't pay attention to it. They didn't want the information. It wasn't used really for much of anything. And so Bill Donelan, to his credit—who was the CFO at the time, said, Here's what we'll do. We'll take the databank deficit, and we'll put it down below the bottom line of the DCRI so it won't count against you in your operational financial reports, and we'll just call it a loss and put it below the line every year, because it was a no-go to try to sell it to anyone else in the institution. You know, if he hadn't done that, we would have had to shut it down. We didn't talk a lot about it, because it would not have been well received, but it kept it alive, and that was on the order of six hundred thousand to a million dollars a year that was just sort of carried. Now, little did I know that they were actually continuing to accrue that negative balance and count it against the DCRI over time, but that came to a head years later. But it kept the thing alive. It was well worth it. Of course what was in the back of the minds of anybody who was knowledgeable about where clinical medicine was headed in the big picture was that healthcare quality was going to be important someday. We had seen it. That leaving doctors sort of to their own to figure out what's right was not the way to go, and now it's come full circle. We are required to publicly report the metrics for how we're doing, and the quality measures that are recorded by the system that a lot of people tried to kill because it cost them money. And we're nationally and internationally known for our quality in cardiology because of that. So that's sort of another key part to the institution. Sometimes institutional leaders knowing when to

make things public and when to sort of get things done behind the scenes that people maybe don't need to know about, that's an interesting component of leadership.

ROSEBERRY: So what is the relationship with the databank now and the DCRI?

CALIFF: (*laughs*) It's still evolving today. It is.

ROSEBERRY: (*laughs*) Still evolving?

CALIFF: Yes. I think over time in the last few years the hospital has done more and more to cover its part. The Division of Cardiology has been more and more supportive. Since Asif Ahmad got here as the head of what's now called DHTS [Duke Health Technology Solutions], the fundamentals of the databank have pretty much been incorporated into the electronic system of the health system. The part that hasn't been covered is the follow-up, which of course the now evolving critical area of health care quality is the outpatient arena. And so we're just sort of in negotiations now to try to understand, I hope, how to offload the costs from our researchers onto the clinical arena where it belongs to and the Clopidogrel drug eluting stent issue is a classic example. We discovered in our own patients that they weren't getting the medical regimen that was right for them with the research data that we had. And the fact that we were collecting this information on our patients allowed us not only to discover it, write a paper that changed the standard of practice, but we were also able to write every single patient and say, Here's something we found out, you need to talk to your doctor now about what to do about it. To me that's sort of the ideal of clinical practice to be able to do that. But at least as of the fiscal year which is about to end our researchers are still carrying the burden of paying for that financial loss. It's hard to get research dollars, so this is a labor of love.

ROSEBERRY: Are there still people from the early days of the databank that are still working today?

CALIFF: We still have a few from the very early days. Bernie McCants, who was around almost in the very beginning, is still heading up the follow-up system. He would probably be the most classical example. Other people who I still run into: Dorothy Brown who was a data technician in the early days and still working in the environment; Frank Starmer interestingly who was there in the very early days is now back in the Information Technology group in the new medical school in Singapore. So I'm in meetings with Frank again after a twenty-five year hiatus; and of course Ed Hammond is over in the business school now as his home, and I still see Ed fairly often.

ROSEBERRY: And are there some who are, who have kind of moved into the DCRI aspect of things?

CALIFF: Well, all the people I mentioned—Bernie, Dorothy—are employees of the DCRI, and of course we still have faculty who were there in the relatively early days. Most of the cardiology faculty are still around and participating in the databank.

ROSEBERRY: Does the work overlap or is it fairly—?

CALIFF: Well, I'd say it's a continuum. You know, when cardiologists or clinicians are using the databank, they're putting information into it. When they're doing research, it's one of the tools they have, but of course there are many—in the DCRI there are many other research tools ranging from the ability to do clinical trials in fifty countries now to these very large registries that we run and then the early human studies that we're now doing that are very important to the effort.

ROSEBERRY: Well, Sir, what have I not asked you today that I should have asked you?

CALIFF: Well, I mean, I think one interesting thing will be to think about the next five years. And we now have new leadership in the Heart Center and the Division of Cardiology. We have a chief information officer for the health system who really sees the integrated electronic health record as the future. We're working very hard on it. So I would expect a real renaissance but in a new incarnation where the databank will really just be part of an electronic health record that covers all aspects of medicine. And the lessons from the databank about informatics and how informatics gets done in the clinical environment will continue to be a key asset, but the look of the databank will be entirely different because we'll be harvesting information from fully developed electronic health records.

ROSEBERRY: I did want to ask you, I meant to ask about the networks that you were developing for these mega-trials. Now, is any of that from the DUCCS [Duke University Cooperative Cardiovascular Studies] organization, or is that—?

CALIFF: Well, over the years the DUCCS organization has had more lives then a cat. (*Roseberry laughs*) And the fundamental construct of people that have done their fellowship at Duke is a vital, ongoing part of the institution, you know, I think has been something that's distinguished Duke: the fact that we don't just send people out there and then forget about them. It's more like the Marines. Once you've been here, you're sort of part of the organization. But the exact physical manifestation of that has varied quite a bit, and it's waxed and waned in terms of it's functioning as a discrete organization. One of the issues that we've always had to struggle with is while there's a strong tie to Duke, the fact is if you're in Chattanooga as a practicing cardiologist, you may have great love for Duke, but the most important thing for you to do in your clinical research may not be

emanating from Duke. It may be emanating from some other entity, either an academic center or a company that's evaluating a product. So the way I like to say it is that clinical research is not a monogamous activity. So there was a time when DUCCS was almost like a military organization and was very self-contained and attached to Duke, and now it's much more of a less self-contained organization. In the future I'm sure like most things there will be a virtual organization, that I hope people that trained at Duke will be a key part of where people's ideas will be connected by the Internet, and being physically present won't be the most important element.

ROSEBERRY: Well, thank you very much, Sir. I really appreciate it.

CALIFF: You bet.

ROSEBERRY: It's been a pleasure talking with you.

(*end of interview*)