

Dr. Clarice Reid

February 28, 2002

Today's date is February 28, 2002. This is an interview between Dr. Valerie Williams of the NIH History Office, who will be interviewing Dr. Clarice Reid, former director of the Sickle Cell Disease Branch of NHLBI. This oral history is a continuation of the interview that was conducted on February 19, 2002.

Williams: I'd like to start with our discussion about treatments for sickle cell disease. So we were talking about the different research approaches, and last time we talked about the globin gene.

Reid: Yeah. That was an approach that I think became more prominent as we knew more about globin gene regulation. But prior to that, I think the initial strategies dealt with things that affect the sickle cell membrane, vasoactive substances, things that affected the polymerization of hemoglobin, recognizing that anything that affected the hemoglobin would require some large quantity of substance to be specific for that.

Williams: Right. What about the oxygen affinity? I think you were saying, like Bertram Lubin, who I'm going to talk to, he did some studies with MET hemoglobin.

Reid: Well, yeah. Things that change the oxygen affinity for hemoglobin were another basic approach. And all these things came from basic research,

understanding that there was more to the sickle phenomenon than just log jamming of red cells.

Williams: Right.

Reid: The initial theory, initial approach, was that all of the symptoms were due to the log jamming of sickle cells not being able to get through the vasculature, and it was more than that. That was kind of like our simplistic explanation of what happened and led to the crises and led to the ischemia and led to all the subsequent organ damage in sickle cell disease.

Williams: I see.

Reid: And, of course, with a more meticulous scientific approach, it was very clear that things were happening inside the cell, and all that led to the whole activity that dealt with the delay, the genetics of delay time and polymerization. So our whole knowledge about that expanded. And also, there were things that affected the transport of ions across the membrane.

Williams: I see. And all of these could contribute to the clinical...

Reid: Yes, right, right.

Williams: I see.

Reid: So we were looking at potassium chloride transport. We were looking at other proteins on the surface of the red cell.

Williams: Okay.

Reid: Uh-huh. So all these things were -- there was just a whole potpourri of

approaches that made scientific investigation very exciting. And that's why I felt that we were always going down several paths at the same time. And each one did not individually lead to necessarily a profound change in what we were doing, but there were explanations that came from that, that as you got more of these things answered or unanswered, it led to other questions, and that's how science progresses.

Williams: So it really wasn't, you know, I had pictured linear.

Reid: It wasn't linear.

Williams: It wasn't linear.

Reid: It's not linear at all. All these things were going on simultaneously and there were proponents of each one of these and bands of investigators working together.

Williams: Interesting.

Reid: Yeah, you knew who was looking at these things at the same time.

Williams: An overlap, I guess.

Reid: Overlap. And everybody . . . And the thing about it, there was a great deal of respect for each approach. I mean, we loved the fact that it was George arguing with Dave Nathan arguing with Alan Schechter. I mean, it was just a, wow, look at this, this tremendous energy, the energy of controversies about these things. And no one had the answer, but everybody respected the fact that everybody had ideas may lead to something. And so we had what we called think tanks. Think tanks were

where we pulled together, led mostly by the architect of our scientific program who was John Hercules, and he pulled all these great scientists together -- I called them the boys' club.

Williams: Really?

Reid: Yeah. Oh, yes.

Williams: The millionaire boys' club.

Reid: The boys' club. This was a scientific sickle cell boys' club. And they would meet in *The Early House* down in Warrenton, Virginia, which is a nice retreat place that had the atmosphere, acres of green land and nice little conference facilities. We ate together, we had roundtable sessions together, and some were playing tennis together, etc. And we had little barbecue things outside. And it was always such a great desire to move the field forward. And John hand-picked these people. I wish I could find pictures . . . You don't need the picture. But anyway, there were people there -- I think at one time Perutz might have come.

Williams: Really?

Reid: Yes.

Williams: So, what was the mix of basic to clinical researchers at the time?

Reid: I think when we first started; I think we might have been predominantly basic. John was a Ph.D. scientist, and he, his orientation was more basic at the time. But that's not to exclude the fact that many of the basic scientists were doing both, were seeing patients and had a great

appreciation for the need to merge one into the other, that basic science by itself, unless it led to something that was going to improve patient care or whatever, was not what we needed to do and put all of our money in that particular arena. So it was that, and there was just a great appreciation for the complexities of science around sickle cell disease. Remember, now, we knew the molecular disease, we knew the genetics of sickle cell disease, we knew the biochemical defect, we knew the DNA mutation, we knew the pathophysiology, we knew the symptoms. We had all of these things more than anything else, but we did not have a treatment or cure. And we had done all the scientific roads to discovery of any disease, you know, the nature of it, and we got all those pieces together, and we could not, after connecting all the dots, we connected the dots but we couldn't come to any one magic bullet. That's what it was; we couldn't find the magic bullet.

Williams: Yeah. That's so fascinating.

Reid: There is no magic bullet. But we always talked about the magic bullet.

Williams: Did you?

Reid: We screened drugs. We tried to make drugs. We did all the little things that we thought were necessary to try to answer the questions about how to get, how to cure and how to treat patients with sickle cell disease. Each one in itself was very enlightening, you know.

Williams: Yeah. It's funny . . .

Reid: And I found all this very exciting. I was like the cheerleader on the sidelines, “Go fight, go fight!”

Williams: You were the ringleader.

Reid: I was the ringleader, yes, between a cheerleader and an orchestra director, you know.

Williams: Right, right

Reid: And since I didn’t have any real basis to join either group, I was just like, “Oh, yes.” They’ll be bouncing things off my head. And I said, “You know what? All of these arguments seem to be relatively sound, but they are a good basis of disagreement.”

Williams: Sure, sure, agreement and disagreement.

Reid: Yeah, yeah. So that’s how I saw my role there then. But out of those meetings, we had a document that laid out an action plan for sickle cell disease for the next five years. We had what we called a five- and 10-year plan.

Williams: Oh. Do you know what it was called?

Reid: The task, the Sickle Cell Task Force Report.

Williams: Oh. I’ll have to look that up. Sickle Cell Task Force.

Reid: Oh, no, Think Tank. I’m sorry. Think Tank Report.

Williams: Oh. You really called it the think tank.

Reid: Yeah. Oh, yeah. The think tank was a, it was an activity people wanted to be involved in. People who got left out of the think tank were on the

sidelines.

Williams: Well, how did you select who was in the think tank?

Reid: Well, John was the leader.

Williams: I see, okay. So he kind of knew who to pull for these meetings.

Reid: Well, he wanted to pull in people who didn't all think alike. I mean, if everybody thinks alike, you wouldn't need it.

Williams: That's true.

Reid: So we had our little fighting groups there who were really pulling together to put their points of view across, and we had Frank Bunn. Frank Bunn may be good to talk to.

Williams: Yeah, yeah. Where is he now?

Reid: He's at Boston. He came to see me in November, when he was here at the study section.

Williams: Oh, okay. Well, I'll look him up.

Reid: They give me more credit than I'm due, but I think -- I'm trying to just not have them give me all this credit. I was just there at the time, and I just had the naiveté to think that all these people were doing exciting things, and I didn't have any reason to try to be supportive or non-supportive of any group.

Williams: But that's a great -- when you can be neutral . . .

Reid: I was neutral.

Williams: That's a great spot.

Reid: And I said, you know, “Science will speak for itself,” and they worked so well. The sickle cell family was so cohesive. It was almost like an extended family. Even now, when we do something, the sickle cell family is so prominent.

Williams: Okay. And why do you think? Do you think it’s just the personalities of the people?

Reid: It’s not just the personalities. It’s the combination of their personalities with the mission. It was a single mission, a focused mission, was what drove these people to be so . . .

Williams: Kind of dedicated.

Reid: Dedicated to this particular problem. It’s a problem that had all the right things there that you could ask all, enormous amount of questions about, incredibly challenging. I mean, you know.

Williams: Yeah. No, I agree.

Reid: And someone asked why did I take this on, because it was incredibly challenging.

Williams: Sure.

Reid: And that’s how everybody saw this. And so they worked together across all kinds of lines, across clinical lines, racial lines. I mean, we were pulling and tugging. But it was a very tight-knit family. It was.

Williams: Okay. So we mentioned the basic researchers, the people who were developing treatment. So, were you?

Reid: Ron Nagel is a very important one to talk to.

Williams: In New York, right. Yeah. He had a recent article that I read.

Reid: There's an article today in *Blood*.

Williams: Oh, okay. I should look for it. I came up with JAMA and New England.

Reid: They were talking about proteins on the red cell, something with membranes. I just saw the title. I just opened it.

Williams: Today?

Reid: Yeah.

Williams: Okay. I'll look that one up.

Reid: Sickle cell is on the cover of *Blood*.

Williams: This month?

Reid: Mm-hmm.

Williams: Oh.

Reid: I'll show it to you.

Williams: Oh, okay. I did not know that. Yeah.

Reid: Yeah. That's a real up. I mean, a sickle cell is on the cover.

Williams: Right. But, yeah, Ron Nagel is one person. Yeah. I know about him. So when I go to New York, I'm going to look him up as well.

Reid: Ron Nagel's laboratory, and the purpose was to examine a selective list of drugs, and he had certain criteria to ask the questions if they do certain things that related to the pathophysiology of sickle cell disease.

Williams: Well, you know, it's interesting you said that, because one of the quotes

from one of the people I interviewed, he said, you know, “After the whole urea cyanate thing, we were really humbled as researchers, because urea in cyanate was sort of real simplistic way going at it.” And he said, “We were just humbled. We had to go back and rethink this whole thing.” And I thought that was a great quote because, you know, when research humbles you, you know, it’s like you’ve underestimated your opponent. You know what I mean? You’ve got to go back . . .

Reid: You have to understand, there was so much excitement about the potential of cyanate.

Williams: Yeah, I guess so. I didn’t know that.

Reid: Oh, yeah.

Williams: People really thought that it would . . .

Reid: Well, we were looking, people were looking for something. This was the ‘70s. Sickle cell disease was going to be life-changing for these patients.

Williams: I see, okay.

Reid: And if you came up with something to do that, you really were going to strike it rich.

Williams: Did people feel like there was political pressure? I mean, did people feel like now sickle cell is in the nation’s eye? We’d better . . . Was there any sort of political pressure to kind of come up with something?

Reid: Well, that was the first disease that had a big federal government program.

Williams: It really was. Okay.

Reid: Oh, yes, and certainly the first genetic disease to receive federal attention. After that, after the Sickle Cell Anemia Control Act, several other diseases were included in the next authorization act, hemophilia, Tay Sachs, so sickle cell led the way for federal approaches to genetic diseases.

Williams: Okay, all right. So, for that reason alone, people had a lot of expectations of it.

Reid: I'm sure they did, yeah. I'm sure what we did, Valerie, is that we raised a lot of false expectations.

Williams: You think? Okay.

Reid: Any time you get a lot of publicity around any issue, around any disease with "money," theoretically you raise expectations of something that's going to be forthcoming that's going to make a difference with the patients.

Williams: Yeah. Okay, then. So there was a sense of false expectation. But at that time, of course, no one had experience with any other genetic disease, so how could you know? I mean, it perhaps seemed reasonable to expect it.

Reid: It was not unreasonable.

Williams: Yeah.

Reid: But, you see, also, the climate at that time was one where people knew very little about -- the people, by people, I mean the public -- knew very little about the disease, and suddenly now we're talking about a disease that affects a significant minority population in this country during the

'60s, when we already had enough things to deal with.

Williams: Exactly.

Reid: Okay?

Williams: Yeah.

Reid: It was like, "Oh, no. Not something else for us again."

Williams: Right, right.

Reid: We need a disease that affects us predominantly. That's how they were saying exclusively, you know.

Williams: I see, okay. So that added more spotlight to it. It's like your own disease.

Reid: Yeah, your own disease.

Williams: Right.

Reid: You have to understand that this is the next book we'll write about all the misinformation about sickle cell trait and disease, and, "Do you have the disease? "No, I have the trait," you know.

Williams: I know. Yeah. That's another, that's a whole 'nother issue.

Reid: That's another issue.

Williams: But, okay. So after cyanate, it sounds like hydroxyurea was the next big one. Is that . . . Or were there others?

Reid: There's a big gap between then and 1994.

Williams: I know, but just, it seems like the other ones never took root like hydroxyurea did.

Reid: Well, hydroxyurea was the result of some careful basic research that was

done to explain, not to explain, but done to confirm the fact about fetal hemoglobin, and there were studies already published in Saudi Arabia. We knew that people with high F levels had very few symptoms of sickle cell disease, so that was well known. So the research question was, how can we either keep fetal hemoglobin being produced or how can we switch it back on? I mean, it was intuitively a question that should have come automatically, as it did, from the research that had been showing that fetal hemoglobin decreased the amount of polymer you had in sickle cell disease.

Williams: Okay, then. But people were working on that pretty continuously, would you say?

Reid: Mm-hmm.

Williams: Okay. So it just took that long.

Reid: And the first part of that was looking at the basic globin gene regulation and expression, how it modulated that. So that was basic research there.

Williams: I see, modulating the globin gene.

Reid: Yeah, and expression, things that modified it. Okay?

Williams: Okay. So, do you know of . . . So, in between cyanate and hydroxyurea, do you know of some of the other major ones?

Reid: Not major, no. I mean, people were looking at things, at platelets, things that just, platelet adhesion.

Williams: Right, right. Yeah, cell adhesion.

Reid: Looking at expanding. But nothing as dramatic as that. We were basically doing symptomatic therapy. We were doing symptomatic therapy. We treated the symptoms.

Williams: Not the true . . .

Reid: No. We treated the symptoms. We treated the acute chest syndrome. We treated the stroke. We treated . . . Transfusions have always been the mainstay. Transfusions never have been off the market, off the table, for sickle cell patients.

Williams: Really?

Reid: That's what we treated them with, transfusions, because if you gave blood with a lot of A hemoglobin, you reduced the amount of S hemoglobin. So that was their therapy all along.

Williams: Okay, okay. But how was that for the patients? I mean, how frequently were they . . .

Reid: Well, they'd have it for a long time. We have kids now who have chronic transfusion programs that get it every six weeks.

Williams: Really?

Reid: Oh, yeah. That's how we prevent strokes.

Williams: Okay. And they...

Reid: I'll tell you about that later. That's how we prevent strokes.

Williams: Okay. So they come in and . . .

Reid: And we give them exchange transfusions or direct transfusions. We try to

keep the hemoglobin S level below 30 milligrams percent.

Williams: Okay.

Reid: So we do that.

Williams: Yeah, because that was . . .

Reid: Transfusions have been the mainstay.

Williams: And still are.

Reid: Yeah.

Williams: To this day.

Reid: Yeah. We still use a lot of transfusions.

Williams: Okay, okay. But I think that's interesting that you mention it. You know, at some point the, I don't know, the focus was more symptomatic: How can we deal with the symptoms as opposed to treatment.

Reid: The focus wasn't on that. That's the reality.

Williams: Yeah, yeah.

Reid: I mean, as we dealt with treating symptoms, people are still trying to find other things along the way.

Williams: Right, right.

Reid: So we never gave up that approach, too.

Williams: Okay, then, okay. So we talked a little bit about that. And we sort of touched on this, but this whole idea that a lot of people felt that research on sickle cell disease was really slow and took longer than it ought to have taken. I don't know that that was something you're familiar with. I mean,

just in reading, I have this binder here of all these different, almost like editorials and things like that, and one of the frequent criticisms here . . .

Well, there are actually quite a few. I mean, first there was the whole screening fiasco.

Reid: Oh, yeah.

Williams: Then there was this whole sense of healthcare priorities. Dr. Robert Scott wrote this piece, “High Prevalence, Low Priority.”

Reid: But that was before the national program began.

Williams: I know. This was before the national program, and maybe that certainly influenced development of the national program possibly, that people thought this. But I think there was just a sense of not being, the disease not being taken quite as seriously. I don’t know.

Reid: Well, first of all, you have to understand that sickle cell disease was highlighted in a political arena. Sickle cell disease affected predominantly blacks in this country. Sickle cell disease had very few blacks working in basic research to attack the problem. Okay? Sickle cell disease research had very limited funding, if any at all, at that time. So there was not a really focused and cohesive approach to sickle cell disease until . . . Even after the national program was established, there were still people saying, “We’re moving too slow.” But how do you measure progress? If you look at the progress that we’ve made over the past three decades, it’s been phenomenal. Have we moved in and done things that have put patients at

risk? You become like a Tuskegee study then. You have to be very careful, if you're doing something that will involve patients in a disease like this, that you do things ethically, morally, sound, and with a good scientific basis for doing that. So I'd rather err on the side of caution. And people are living longer, more productive lives, and we still don't have a cure.

Williams: Right.

Reid: I mean the fact of the matter is that one of the things you have in here about sickle cell, if nothing else had happened in 1974 or '75, whenever we got underway, that was the first time in this country that we had a comprehensive approach to care. Patient will see you frequently and on a personal level and not episodic, fragmented care in emergency rooms. That in itself led to more longevity and increased quality of life than anything else. I mean, before we got hydroxyurea that was already established. Go talk to Dave Nathan. He'll tell you that. If nothing else happened in this country . . . Because it was not just the 10 sickle cell centers that were funded directly. All the other centers took that as a model and began treating their patients in similar ways.

Williams: Oh, really?

Reid: Oh, yeah.

Williams: Okay. So the influence of the centers went beyond just the 10.

Reid: Oh, yeah, absolutely.

Williams: Well, you know . . .

Reid: You didn't have just the 10. You have all these other centers, because we put out protocols of care.

Williams: Okay.

Reid: We told patients what to ask for when they went to an emergency room.

Williams: Oh, really?

Reid: Little babies had their own little book. It had notes such as "take my temperature, here's my hemoglobin." Yes.

Williams: Okay. Oh, this is amazing.

Reid: Not many people sit up and take notice of clinical care.

Williams: I see. Well, I'm glad you moved into that, because I really did want to get back . . . We didn't talk about this as much about the centers.

Reid: I mean, the centers were not at the forefront of pushing the envelope of basic and clinical research initially. They were at the forefront of bringing the community groups together; which never were brought together before to attack a problem that was common in the minority population; make them work across all these boundaries. Yeah. You couldn't have a center if you didn't have a black advisory committee. Somebody says; yes, to look at what you wanted to do to the patients. They weren't scientists necessarily; community people. They were watchdogs.

Williams: Right, to make sure that things are being taken care of. Who masterminded all of that? I mean, I know you were definitely involved. But who kind of

masterminded the vision of the centers?

Reid: Well, that was done before I even got there. I came in as the centers had already been organized. I think it was the first National Sickle Cell Disease Advisory Committee that was appointed by then Richardson, who was head of HEW, and that committee came up with the fact that we need a program that has four components, but he wanted to have basic and clinical research, he wanted to have comprehensive sickle cell centers with the patient as a focus, we need a program that has education, and one that has screening and counseling. These are the components of the national program. And they all had to be together to run the center.

Williams: Okay. And do you know why they said 10 initially?

Reid: They didn't say 10. We had 15.

Williams: Oh.

Reid: Ten was established in 1983 in the Omnibus Act that . . . What was that act? I want to say Budget Reconciliation Act. No, Orphan Drug Act of 1983.

Williams: Oh, sure.

Reid: Okay? It didn't say we had to have 10. We have to have a minimum of 10.

Williams: I see. Okay.

Reid: We have never had more since then, but we had to have a minimum. There is no ceiling; there's a floor.

Williams: I see.

Reid: We've been at the floor.

Williams: All right, then. But, so, would you say it's been as many as 15.

Reid: It was 15 initially.

Williams: Okay, okay. Do you know how large . . . I mean, what's the maximum number that they have funded?

Reid: Fifteen.

Williams: It has? Okay. It is 15. Okay.

Reid: At one time.

Williams: But currently, there are 10.

Reid: Right.

Williams: For the 1998 to 2000?

Reid: We've had 10 since 1983.

Williams: Okay, all right, then.

Reid: Or 1980, somewhere in there.

Williams: Right.

Reid: We only had 10.

Williams: And since then, that's the combination of programs that have been renewed for another five years?

Reid: Some for 10 years, some for 15.

Williams: Okay, then . . . And also new folks coming.

Reid: Coming in.

Williams: Okay, then. And we talked a little bit about . . . I looked for an RFA. The only one I found was for; I think it was '98, about the criteria and the selection process and all of that.

Reid: Go ahead. I think you should have '96-'97. The one in '98 is the last one that I was involved in; '97 I think.

Williams: Maybe . . . Okay, wait a minute. Okay. This is not it. This is something else. This is the only thing that I have. This is from the NIH guides

Reid: Well, that's last year.

Williams: Yeah.

Reid: It has whole new components now.

Williams: Okay. Okay, then.

Reid: You need to find one going back before then. This has taken a whole new structure, I understand. I haven't read this. It's now the hybrid of the other sickle cell centers with a network piece, trying to integrate it.

Williams: Okay. So this wouldn't necessarily be representative of what it was . . .

Reid: Now.

Williams: Okay, all right.

Reid: That's the new hybrid.

Williams: And what I've been trying to look for and I found one, but this is an example of what the new Sickle Cell Disease Advisory Committee and that's '98.

Reid: Oh, yeah.

Williams: Some of that stuff is available on the Web.

Reid: Oh, is it?

Williams: But I don't know if you think . . . I mean, I can try to track more of those down if you think that might be an interesting . . .

Reid: No. You just need to take it from me that the national committee recommended all these pieces.

Williams: Okay, all right.

Reid: All the minutes should be available someplace.

Williams: Yeah. That's what I was thinking. So I'll see what I can do.

Reid: You should go to NHLBI, to their Information Office, and maybe you could get those.

Williams: Okay. I mean, first . . .

Reid: I don't how far back they're going to go.

Williams: That's the problem. I mean, some things, the NIH History Office is collecting from each institute things they want to get discard because they don't have space.

Reid: Yeah. I think when I left; I sent some things went over there. I'm not sure.

Williams: Right. Well, we have a big stack from NHLBI. It's huge. I haven't gone through all of it, but I would start there, and I didn't know if they kept their old records. So, in any case, the Orphan Drug Act.

Reid: Yes. I think '80, '81, somewhere in there. It was legislation that officially

legislated sickle cell centers.

Williams: Okay. And maybe you could tell me a little bit about this orphan-drug status. I've seen this around. Do you know much about that, or is that something I should . . .

Reid: You'd have to get more details about that from FDA. Orphan-drug status was a program initiated, I think, at some point that allowed people who proposed clinical research in diseases that were considered orphans that had patients less than X number -- it might have been less than a million; I'm not sure -- and the drug companies and people get special recognition for doing that. Either drug companies would get a tax kind of thing, something like that. I don't know the status of that now.

Williams: Right. And I haven't . . .

Reid: But orphan diseases were described, and they're listed. There's an orphan-disease booklet. You have an office at NIH of orphan diseases.

Williams: I know, right.

Reid: So that tells you those diseases. And that act, at that time, was addressing research with those diseases. And the point then was just to give them an added advantage because they were small diseases without advocate groups, to go down on the Hill and legislate for those small diseases and give them an opportunity to compete in the marketplace.

Williams: Right, and the funding stream. Now, speaking about political advocacy, tell me about some of those groups. I know there's the sickle cell,

SCDAA, and there's another one out of Los Angeles, I believe. I mean, there are a few of them. Can you say anything . . . ?

Reid: Well, there were a lot of them earlier.

Williams: Right.

Reid: And in the early '70s, there were a group of programs funded on the service side, screening and education clinics, and most of those had some type of community group associated with those. And as those clinics became phased out, the National Association of Sickle Cell Disease was always there. This was started at the same time as the national program by Charles Whitten. He's in Detroit. Okay?

Williams: Oh, yeah.

Reid: Talk with him.

Williams: Okay.

Reid: Okay. So his organization became the umbrella for all these other groups, and they all now moved to organize under the SCDAA. It used to be the National Sickle Cell Disease Association. Now it's SCDAA. Okay? So his became the umbrella for those so they could maximize their opportunities for being successful.

Williams: I mean, many diseases have political advocacy groups. Were these pretty powerful ones? Did they have an impact?

Reid: I don't think we've ever had the impact of others. We haven't had the impact of a hemophilia group, an anemia group. And I'm not sure what

that means or what that says. I think, first of all, we have not had the political power of persuasion that many of these other diseases had with the representatives they had already on the Hill. And sickle cell disease, because it affects such a small population, predominantly blacks in this country, has not had the support, the bigger support than other diseases. And I have to tell you that there are even fewer numbers of patients with an anemia, but they've got a much bigger, powerful lobby. Okay? And it's all how you work the system. We have a very, very strong supporter when we had Lou Stokes on the Hill.

Williams: Oh, really?

Reid: Oh, yeah. He was Mr. Sickle Cell Disease.

Williams: Yeah. Well, certainly one of the quotes that I read is sickle cell disease is sort of, it's not your cousin's disease. This was Trimble.

Reid: Oh, yeah. He said that.

Williams: Yeah. It was in *The Scientist*, and they were asking him, you know, what are some of the factors that you think has to do with how much attention is being paid for, and he said, "You have to remember, for a lot of congressmen, some of these diseases are like their cousin's disease. There's someone in their family that they can directly link to it," and it gives it a natural attention. But sickle cell -- it's not your aunt, it's not your cousin, and . . .

Reid: You may not hear a lot about it until somebody brings something to your

attention.

Williams: Right.

Reid: There's nothing to denigrate the congressional people, but you have to be realistic about it. People deal with the diseases and the entities they know about, those that are brought to their attention to highlight.

Williams: Exactly, yeah, and I think that's kind of what he was saying with that statement, that it's something that, if it's something they can affiliate with immediate family members, it's . . .

Reid: But, you see, they have to translate that even more. A sickle cell patient, even though it's not your cousin's disease, requires a lot of the health resources in this country. Therefore, it impacts on everybody else's disease, everybody else's health status. But if you can remove, if you can decrease the amount of care needed for these patients by proving other things happen with these patients, it benefits all of us.

Williams: I see, right, right.

Reid: In the public health arena. It's a public health problem.

Williams: Right, it is.

Reid: It doesn't matter how many patients, whether they're in your group or others. It's a public health problem that affects all of us.

Williams: Yeah. It's not solely limited to . . .

Reid: HIV affects all of us. I don't have it. I mean, it affects everybody. Resources are needed for that group of patients. If we can do something

about that disease, it impacts all of us.

Williams: Sure, sure. So, in terms of the centers and funding, how did . . . I mean, did funding increase over time for the sickle cell . . .

Reid: I mean you have to look at that and ask the question of NHLBI. The funding went up, and then it went down. It hasn't gone up proportionately to other diseases in the institute, I don't think. I think we get to a level and we seem to be there and stay there or we go down. If you look at the trend, it hasn't been the accelerated -- it hasn't accelerated consistent with the amount of science that we know about the disease.

Williams: Oh, okay. That would be an interesting chart. Yeah.

Reid: We'll get the chart.

Williams: Yeah. Knowledge versus funding, what we know.

Reid: What we know, what we need to know, and how we get there.

Williams: Yeah. Although I guess one could argue, the more you know the less resources you need to give to it because there's been more, there's been so much money poured in to get to a basic...

Reid: Well, I hate to always compare diseases. I mean, that's a problem I fall into as a doctor. I think when people say, "Well, are you getting enough?" I say, "As compared to what?" There's never enough of anything. I mean, early on in the initiation of the sickle cell program, people would always say, "Well, hypertension is more important in blacks than sickle cell disease." I said, "Well, I don't get into what disease and what is more

important.” I said, “Equally, each one is equal of attention and funding.”

Williams: Yeah.

Reid: So you get into this playing one disease off against another, you know. As a physician, I find that to be very unpopular.

Williams: Well, it’s difficult. I mean, there’s no absolute answer. One of the things I thought to do with the study is try to do a comparison with another single gene-mutation disease like cystic fibrosis.

Reid: Cystic fibrosis.

Williams: But I sort of felt like you did. How would I really make this comparison? I mean, what aspects of the disease would I be comparing, and . . .

Reid: Also, the numbers are different. I mean, how many are you talking about with cystic fibrosis?

Williams: Oh, I don’t know. I think it’s a little bit higher.

Reid: I think it’s higher, too.

Williams: Yeah. But, anyway, I . . .

Reid: Sickle cell disease is the most common genetic disorder affecting, one in 450 black births.

Williams: Right.

Reid: I think you’ll find it’s still the single most common one, you know, PKU and cystic fibrosis and sickle cell anemia and all these other diseases, you’ll find that to be true.

Williams: Okay. Yeah, it’s a thought. Like I said, I don’t know if I would do that,

but it's something to think about.

Reid: Well, another thing you think about, you may want to do it from the point of view that there's very little attention by the pharmaceutical industry in sickle cell disease because there's nothing for them to make money off of.

Williams: Yeah, right.

Reid: And they're in the business of that.

Williams: Right and I guess that's why you need the orphan-drug status, because . . .

Reid: I don't know how active that is anymore. I don't know whether that's still applicable or not.

Williams: Now, we talked a little bit about clinical trials and the importance of the clinical trials. Maybe we could review some of that information, some of the key clinical trials in sickle cell research, and sort of the consequences of the . . .

Reid: Well, the first one was [hydroxyurea] the second was cyanate. You're talking about drug clinical trials.

Williams: Mm-hmm.

Reid: The next one, the real next clinical trial that was the highlight of turning around morbidity for children with sickle cell disease was the Penicillin Prophylactic Study, and that was in the mid-'80s. That was a study that asked the question, can we prevent early morbidity/mortality in infants and children with sickle cell disease by giving them oral penicillin prior, in the first six months of life and doing it on a regular basis? And we

randomized the study for patients, children, to receive penicillin and a group that didn't, and I think the study was stopped about maybe a year early because I told you before; we lost approximately three children in the untreated group and none in the treated group. They were dying from streptococcal pneumonia; strep pneumonia was the organism. So that was the turning point in the treatment or prevention of complications from sickle cell disease in the pediatric population.

Williams: Okay. And sort of what precipitated that study? Why did they decide . . . ?

Reid: Well, it wasn't they decided. It was Dr. Marilyn Gaston came here from Cincinnati, my deputy. She'd had -- there was a potential project. It was not just an idea, had not been given any thought before, but we'd never had an opportunity really to demonstrate that. And we had set up this network of patients in the CSSCD, and we had an organized approach to clinical research for the first time through the Cooperative Study of Sickle Cell Disease when we enrolled 4,000 patients, infants and newborns through whatever, that we had a structure to do that.

Williams: I see, okay.

Reid: So that was one of the earliest studies that came out. And from that study, NIH had a Consensus Development Conference that recommended, based on that study, that all newborns should be screened at birth for sickle cell disease.

Williams: Right, right. And that was across all racial . . .

Reid: All races, yeah. Initially, a lot of them said the universal screening is not cost-effective, we should just look at targeted screening, looking at kids who are predominantly black, who are at risk for that, and, of course, we don't always know who's black. And because we do know that the gene crosses other ethnic groups and many of the states that had low numbers of blacks had significant numbers of sickle cell patients.

Williams: Really?

Reid: Well, this gene is of a Mediterranean origin.

Williams: I know, right.

Reid: It is not necessarily what you see. And a lot of our infants at birth do not look black anyway.

Williams: That's so true.

Reid: And black is who you say you are. Your race is who you say you are.

Williams: Right, right, that's true.

Reid: So, anyway, newborn screening is probably now about 46 states in the country. So that was kind of like the turning point for pediatrics, that particular study. That was a landmark penicillin trial of the '80s, and that received media attention, pediatric attention across the country. It was a landmark study. It saved lives.

Williams: But you raise an important point. I mean, it was because of the organized structure of the cooperative, you know, the CSSCD. Had that not been put in place . . . ?

Reid: We had that in place, and, see, the penicillin study was a piece of that. Some patients in that who were already enrolled participated in the penicillin study.

Williams: Okay. Now, who would I talk to about the CSSCD study?

Reid: Me.

Williams: Okay, all right, okay.

Reid: That's this book right here.

Williams: That is it. Okay. And you masterminded sort of the -- I shouldn't use the word mastermind, but that was sort of your vision, that there should be some way of tracking . . .

Reid: That's the penicillin study right here.

Williams: I see.

Reid: What year was that?

Williams: Eighty-six.

Reid: Eighty-six, okay.

Williams: Okay, then.

Reid: That's why I wanted you to read this.

Williams: I should read that.

Reid: No, no, no, no. You can just look at it now. When I came at the first ASH meeting in 1975 or '74, I met with Tony Cerami and Tony is the one who said that, you know, "You cannot establish a research program in sickle cell disease without knowing the natural history of the disease." So I kind

of summarize that there.

Williams: I see.

Reid: Why don't you turn it off and read it real quick.

Williams: Yeah, that's a good idea. So the CSSCD was a landmark in sickle cell disease research, and you say that this idea sort of came from a conversation with Cerami.

Reid: Well, it wasn't the idea came from him. It was the challenge came from him. The idea was already there that in order to know the cause and effect of any drug and how it impacts on a symptom of a patient, you need to know the natural history of the disease itself. And everything we knew before this time was anecdotal and retrospective. There were no prospective studies of any of the course of sickle cell disease published anyplace. Everything was anecdotal and retrospective in nature. So it was natural that you needed to know this important information in order to propose strategies, in order to know whether what you were doing was effective or not, and his was kind of an indictment of the program for not having done that when I was coming on the forefront.

Williams: Oh, really?

Reid: Yeah.

Williams: Okay.

Reid: And it turned out that at that time there was something in place called the Hematology Study Group that was organized by Dr. Wendell Ross at

Duke University, which had outlined many of the components of the natural history study, but it had not -- it was a contract, but it had not surfaced as a major project in the Sickle Cell Disease Program. It turned out that NIH every year was transferring about \$3.5 million to HRSA to support the screening and education clinics, and this was causing a lot of consternation among the research environment, that we're taking NIH funds and giving those over to HRSA to support screening and education. At the point in time when NIH stopped doing this and HRSA got its own appropriation, the House language stated that the \$3.5 million will be kept at NIH to support a clinical study.

Williams: Oh, wow!

Reid: So we had it. It was not a voluntary "let's go do this."

Williams: I see. Genius at work.

Reid: So we had to structure it to develop, but now we had the resources to do it, which had never been available before. And this study underwent more reviews than you can imagine getting it going.

Williams: Really?

Reid: Yeah. Well, there were a lot of "doubting Thomases" that we could organize anything like that. We had too many questions to ask. Are people going to really work together? Are patients going to really do all these kind of things that we were requiring in the protocols? So I think there was a degree of quasi-support but a lot of ambivalence about the

whole study. We had to take it to counsel several times for review and re-review.

Williams: Really? Okay. But people understood the importance of doing a study like this. Right? Would you say?

Reid: I think the importance was there. I think the questions were asked whether we had the capabilities of doing that.

Williams: Okay. Implementation.

Reid: Yeah.

Williams: Could you really implement a program like this?

Reid: It was big; it was a big study.

Williams: Okay. How many sites were involved?

Reid: We started with 23 sites and 4,000 patients.

Williams: Oh, wow. That is.

Reid: But, see, they underestimated the perseverance and tenacity of the people in the branch and the sickle cell community outside to want to do this.

Williams: Okay, then. And these 23 sites were they all voluntary?

Reid: Well, they competed.

Williams: They competed to get . . .

Reid: You couldn't select them *a priori*. They were all competitive sites directed by a review process and all that.

Williams: Okay.

Reid: They had to demonstrate the capability of doing this review process.

Williams: Right. But I guess in terms . . .

Reid: It would have a certain patient population. You could have five patients and be in the study. We had a minimum number of patients, adult, pediatrics, and you had to have a lot of things in place to do that, and the institutional support that you needed to do that also.

Williams: Right, because it would take a lot of resources to participate.

Reid: Manpower, patients, laboratory, cooperation at the institutions where you work.

Williams: Okay. Now, but in terms of the patients, did they volunteer?

Reid: Patients were very eager because, remember, all patients in clinical trials ultimately get better care.

Williams: Really? No question?

Reid: All clinical trials, I don't care whether it's sickle cell disease or whatever, most of them are going to get better patient care. And certainly, black patients, having gotten poor care, had nothing to do but gain to be in a study. They were anxious to be in a study. People love them. People were taking care of them for the first times in their lives. They enrolled and they stayed there.

Williams: Okay. So, getting the patient population was not difficult.

Reid: Patients with sickle cell disease, they'd come.

Williams: Okay, then.

Reid: They were getting no care.

Williams: Yeah. You know, I keep hearing this.

Reid: Clinical research is the ultimate for getting good clinical patient care.

Williams: Yeah, you're right.

Reid: I mean, you'll hear a lot of people with cancer say, "Listen, I'm going to sign up in this clinical trial."

Williams: Because I know I'll get the care. It's true. The degree of attention that had been paid to sickle cell anemia. One might expect correlation between the care of the patient and the degree of attention.

Reid: Well, I don't know if that's necessarily . . .

Williams: A valid point.

Reid: Attention does not always equate to care. Okay? Not to good care.

Williams: Yeah, not to good care.

Reid: But they've got that within the studies, you know. Within these studies, they know they're in an environment of personal attention, care, follow-up.

Williams: But really, though, there's no sense of concern about exploitation?

Reid: Exploitation by whom?

Williams: By investigators of the patient. I mean, one of the things that I always wondered is, after Tuskegee...

Reid: This is not doing anything that's invasive to the patients. I mean, they're coming in to get weighed, they're coming here with their problems, and they're coming and meeting with nurses and physicians. We don't have

anything invasive to do to patients. We're not withholding on medication.

Williams: I see. Strictly just monitoring, measuring, following the patients. Okay.

Reid: Yeah. We didn't have anything, we didn't have any drugs or anything that we were giving patients and none were being withheld, so it was not the same. The natural history study was just looking at clinical parameters over the course of time.

Williams: Okay, then. But, obviously, they were getting some sort of treatment. Right?

Reid: Well, the treatment. Yeah. They would get the supportive treatment they needed. They would get transfusions, they were getting -- if they had a complication of some sort antibiotics, they would give them that. But outside the clinical trial, if they were in there, they may not have the physician to call to even get that.

Williams: I see, I see.

Reid: Yeah. Because we took care of them whether they were in the trial or not, but, clearly, those patients were being seen more frequently and known by their physicians, their course was known. It was that kind of relationship, the personal relationship they got.

Williams: Okay. So it wasn't like the standard clinical, let's try out something on this population and see.

Reid: Oh, no.

Williams: It was really just to . . .

Reid: These were not treatment protocols.

Williams: I got it.

Reid: No. These were just management protocols.

Williams: I see, okay.

Reid: The only treatment part of the whole CSSCD was the penicillin study. Everything else was clinical parameters.

Williams: Okay. Well, that makes it a lot clearer for me.

Reid: It wasn't a clinical trial in the true sense. The CSSCD is not a clinical trial. A clinical trial always has an arm of the true clinical trial where you're offering to ask the question, is this better than the other.

Williams: Exactly.

Reid: No. So this is not a clinical trial per se. In a true Phase II clinical trial, Phase III, this is not it.

Williams: Okay.

Reid: Now, the hydroxyurea is a Phase III, and I'll tell you about that later.

Williams: Okay.

Reid: This is just a management . . .

Williams: This is a management trial. Okay, then. So it's not analogous.

Reid: This was a feel-good study. Okay?

Williams: Okay. Management trial. Okay. I want to make a note of that.

Reid: Management study.

Williams: Management study. Well, I know you have to go at three. Okay, then, all

right.

Reid: I need to be somewhere at four. I've just got to get back on this stuff.

Williams: Okay, then.

Reid: But you have to understand about the CSSCD. Now, all the papers here you'll see, none of these are giving the patients anything. They're looking at leg ulcers, the symptoms and how many are there, and they're just... these are mostly statistical stuff, mortality. We looked at people, how many have died over a period of time, and found out that within the study now, the sickle cell patients were living longer lives. The initial study that came out in the '70s and '60s, most of them died by 25. Our patients were living, the average age for females was either 47 and for males 43. You'd have to look at that paper.

Williams: Okay.

Reid: And we had one for pediatrics as well. We showed that pain events, the more pain you had, the more, the less, the more likely we were to have early death. So we showed that relationship, pain. We showed that high fetal hemoglobin reduced the pain rate. So these were the kind of studies that came from that.

Williams: So I guess, if I could look this up, I could find out all the different . . .

Reid: Non-therapeutic.

Williams: Okay, non-therapeutic.

Reid: By definition.

Williams: Okay. And I guess, you know, the title sort of says that. It's just that whenever you think about it in this climate, you think about trials, you think always about treatment. But this is not therapeutic.

Reid: This is natural history.

Williams: Natural history.

Reid: Following the course of a disease over time.

Williams: And had they done this with other diseases prior to sickle cell? Do you know if there have been any other natural . . .

Reid: I think we had the natural history of rheumatic fever when I was in pediatrics years ago.

Williams: Oh, really?

Reid: Yeah. I mean, I don't know whether there was a trial or not, but we knew lots about that. We knew the natural history of a lot of diseases, but none had been organ . . . I mean from other cohort studies a lot of diseases. You can have any organized cohort study to ask questions of sickle cell patients.

Williams: Right. But certainly the idea of the natural history . . .

Reid: Of a disease process is important.

Williams: It is important. And it's something that most people see as being important. So when we talk about, going back to your point about the fact that there were a lot of questions about it, about the implementation, maybe you can tell me more about the issues. You said that there were 23

sites, 4,000 patients.

Reid: Yeah, pediatric and adult populations.

Williams: Right. So what were the critics or the “doubting Thomases” thinking, that people would drop out of studies?

Reid: Well, just think we had an enormous number of questions we tried to answer, and the critics were right about some of them, that we were trying to get too much information, and sometimes when you acquire too much information, you dilute the importance or you dilute the validity of what you’re getting.

Williams: Okay, then.

Reid: And perhaps they are, I won’t call them “doubting Thomases”, the questions they raised were legitimate.

Williams: Okay.

Reid: We were embarking on something of this magnitude and had not done this before, and I think they wanted to make sure that we were getting it right. There might be some who objected to us getting the dollar amount to do this. I’m not sure whether it was ever stated or not, but I’m sure that could have been part of it. But I just think a lot of them wanted to make sure that we were going to get something for our investment.

Williams: Because it was a sizable investment.

Reid: It was a sizable investment. It required people who had not been working together in a field like this before . . .

Williams: To come together.

Reid: To come together.

Williams: So, during the first . . .

Reid: It was the best-run study, very little dropout, great retention of our patients.

Williams: Okay, right. So in the first two or three years, how did it go?

Reid: It was fine. Well, the first two or three years, we were busting ourselves, trying to get a data-coordinating center and get organized the first two or three years, with just organizational problems. But we had a wonderful leader, Wendell Ross, our overall study chair. And it went smoothly. I mean, the benefits reaped from it were so great that I couldn't even remember the hassles and the pulling and all.

Williams: Really?

Reid: Oh, yeah.

Williams: Okay.

Reid: And you had manuscripts. Everything had its own set of issues and problems.

Williams: Right, right. But overall...

Reid: But you develop a cadre of clinical physicians who were very caring, who respected each other, who worked together, and they were very excited about what they were doing.

Williams: Now, did the centers participate in this as well?

Reid: Not as centers themselves, but some of the PIs. I mean maybe three or four sickle cell centers did. I'm not sure. But that's not a requirement for them. Some of the center patients were in the CSSCD, yes. They could apply, too.

Williams: Okay. I wasn't sure if that was a separate . . . But the centers were in the CSSCD.

Reid: Some were, yeah.

Williams: Okay, then. So, and it's largely been a successful venture.

Reid: A very successful venture by all measures.

Williams: Okay, then.

Reid: And everybody will refer to that study when they are when they are trying to plan other therapeutic studies.

Williams: I see. They'll go back to the information that was gathered from that study. Okay. And each year, all the information was published and made publicly available.

Reid: At annual big meetings and it was a wonderful, wonderful place for that.

Williams: That's magical, yeah. That's golden. So kind of going back, we had the CSSCD. What were some of the other -- and I shouldn't say clinical trials.

Reid: Oh, yeah. We do have clinical trials now. After the CSSCD, in '94, Sam Charache the clinical trial of hydroxyurea, and the importance of that study was to find out if hydroxyurea could reduce crises -- I don't want to call them crises -- painful episodes by 50 percent. That was the question.

Williams: By 50 percent?

Reid: Reduce it by 50 percent. And it was a very well-designed, simple, randomized study in which you had the placebo arm and the drug arm. And, again, that study was stopped short because they demonstrated very early that they could reduce painful episodes. Not only that, they reduced the number of hospitalizations for the chest and they reduced the number of transfusions that patients required. So we sent out a medical alert, general medicine, and they allowed you to sign a medical alert. Sometimes you can't publish data in advance, but we published it in advance so doctors would know about that.

Williams: So this was the next sort of big event.

Reid: Yeah, and that was for adults.

Williams: I see, okay.

Reid: One is going on now with pediatric patients.

Williams: Okay. And in terms of its mechanism, are people still thinking that it's increasing the amount of fetal hemoglobin?

Reid: Some of the patients got better who didn't even get an increase in fetal hemoglobin.

Williams: Okay, then.

Reid: And I think people think it has something to do with the type of red cells that affected other things as well.

Williams: I see, then.

Reid: You need to talk to Alan and all those about that.

Williams: Right. But for the most part . . .

Reid: For the most part, it met that criteria by increasing fetal hemoglobin and patients are doing better. I understand there's a paper coming out now to show that patients are living even longer. Marty Steinberg up in Boston I think has published a paper. These adults have been on hydroxyurea now since probably 1996 or '97.

Williams: Oh, okay, early, right from the beginning.

Reid: Late '90s, yes. So you've got about at least a five-year follow-up of patients.

Williams: Okay, for that study.

Reid: Mm-hmm.

Williams: Now, before hydroxyurea, though, there was 5-azacytidine.

Reid: The 5-azacytidine was not a real study. That was a drug -- that was the first drug that was shown -- I don't know what animal model they used, but it was in chimps or something.

Williams: Yeah. I think it was in the baboon.

Reid: Baboon, right, that showed that 5-azacytidine turned on fetal hemoglobin, but 5-azacytidine was toxic and it couldn't be used.

Williams: Okay, then.

Reid: It was like a pre-hydroxyurea. There were a lot of agents that turned on fetal hemoglobin, but they could not be used in patients because of their

side effects.

Williams: I see. And that's always been a problem with sickle cell research.

Reid: Well, even so with hydroxyurea because a lot of that drug was used, I won't say exclusively, but a lot of patients developed PCV [packed cell volume].

Williams: PCV.

Reid: And patients in that study, a few of them might have had some chromosomal effects from that, but I'm not sure. We were worried still. We monitor our patients very closely. And there was some concern about the long-term effects of hydroxyurea based on the studies. And, therefore, patients who were in the hydroxyurea study are still followed by NHLBI. They're in a follow-up study called MISH.

Williams: MSH.

Reid: MSH. MSH [Multicenter Study of Hydroxyurea] follow-up study.

Williams: Okay, okay.

Reid: And I don't know where the data come from that or not. But not only that, people worried about this drug being particularly carcinogenic.

Williams: Okay. So there are questions about this treatment.

Reid: But we did it in patients who were severely affected with sickle cell disease, so that was the criteria for that entry, as I recall. Patients had to have a minimum of three painful episodes a year that required hospitalization.

Williams: Okay. I see.

Reid: So we selected the most severely affected patients for the study. So hydroxyurea is not for everyone and they have to be followed closely by their physicians. And I understand right now there's one for pediatric patients that's ongoing.

Williams: Okay. So you have pediatric and adult populations.

Reid: The study that's published, the clinical trial was for adults only.

Williams: Okay.

Reid: And that was the first drug. We have -- I'm trying to think of the name. Squibb, in its drug, the drug announcement, included sickle cell disease as one of the diseases treated by hydroxyurea.

Williams: I see. Okay, then.

Reid: We used their drug announcement to treat sickle cell disease. So that was the first drug named by a pharmaceutical company to treat sickle cell patients.

Williams: Really? Okay.

Reid: And everything else you mentioned has been out there, but none of them have ever had a drug company include that in their diseases for treatment.

Williams: Really?

Reid: Cyanate was never listed, hydroxyurea, and all those other little things, not listed.

Williams: Oh, okay. Wow. So the drug companies are sort of very late in the sickle

cell disease game.

Reid: Well, this is their drug and they gave us this drug. They allowed us to use it.

Williams: I see. Okay, then.

Reid: They provided the drug free.

Williams: I see. Okay. All right, then.

Reid: It's like Wyeth gave us the penicillin free.

Williams: I see.

Reid: In clinical trials that involve a drug, you have to work with a drug company to use their drug for this purpose.

Williams: Right, okay. So Charache was the one who initially had the contact with Squibb? Or do you know how that happened?

Reid: Probably did. I'm not sure. You'd have to ask. All of us probably had some contact. He was the one who proposed the clinical trial that went through review at NHLBI and got funded. He was at Hopkins.

Williams: Okay, right. I'm familiar with him and have read a little bit about that study.

Reid: The last clinical trial was the clinical trial of stroke prevention. That was done by Bob Adams at the Medical College of Georgia. That was probably published in 1998. In that study, what he used was something called Transcranial Doppler. First of all, let me tell you that children with sickle cell disease have a high prevalence of stroke in the first decade of

life. So he proposed that if we could find a way to determine if vessels, cerebral vessels, had increased resistance to flow, we may know children who are at risk for stroke. Okay? You can examine vessels in the neck that show there's increased flow, decreased flow, and something there may be indicating increased risk of stroke. So he used the Transcranial Doppler, screened children at many, many centers, and he had a cutoff point of I think 200 centimeters velocity. You'll have to look it up. Anyway, those over that were randomized to get on transfusions and not, and he put, those on transfusion prevented strokes and those who didn't, there were a number of strokes in that group.

Williams: Wow. Okay.

Reid: That was called the stroke study.

Williams: Nineteen ninety-eight.

Reid: Mm-hmm, Robert Adams.

Williams: Okay. From Medical College of Georgia.

Reid: Mm-hmm.

Williams: Okay.

Reid: So there were a lot of things just coming out, flowing out at the time.

Williams: Right, right. Well, this is sort of the '90s.

Reid: Yeah. It was in the '90s.

Williams: Right. This is recent.

Reid: This is three years ago.

Williams: Yeah. I mean, so just thinking about the decade and the time period.

Reid: It fits right in.

Williams: It fits kind of right in that the '90s have now really come back to . . .

Reid: It was called the STOP Study.

Williams: The STOP Study.

Reid: Uh-huh, s-t-o-p.

Williams: As in stopping strokes?

Reid: Yes, stroke.

Williams: Very clever.

Reid: They're doing a STOP 2 trial now. I don't know what the question is. I think they're trying to see, can they stop transfusion in three years or use less blood or something.

Williams: Okay, then.

Reid: So there's all very good questions they're asking. The STOP 2 trial is now going on.

Williams: And a lot of it is preventive in nature.

Reid: Oh, yes.

Williams: And not to say that there still isn't the look for a cure.

Reid: Right.

Williams: But, you know, like you said, you've seen people looking for what are some indicators, and you suggest that the following course...

Reid: I think the whole thing now is looking at polymorphism of genes, about

that. All sickle cell disease patients, you're going to see the same mutation. But why are some people very severe and some are very mild? What are the differences? So we could find some molecular markers and find out who's going to be and who's not, then you'd have a better way of using some of these invasive therapeutic approaches with these patients. Everybody does not need the same approach. We don't know how to select patients out. Bone marrow transplantation is very good. I mean, we haven't talked about that either.

Williams: Right, right.

Reid: Gene therapy. All those little things. And now they're doing bone marrow transplantation, so you don't have to replace all the sickle hemoglobin. Okay?

Williams: Yeah. I know.

Reid: That's exciting.

Williams: Yeah. And I was going to say, it seems like the hope is really on bone marrow transplantation.

Reid: Yeah. We funded the big bone marrow transplantation study up at Seattle, at the . . .

Williams: Hutchison?

Reid: Yeah, Fred Hutchison Center. And the person who was doing that is Keith Sullivan, who's now at Duke.

Williams: Okay, Keith Sullivan.

Reid: Yeah. He's no longer with that study. They published good data. We showed that we could successfully transplant children with sickle cell disease.

Williams: Okay. I know the risks are pretty high, though, for that one. Isn't it, for bone marrow transplantation? There may be rejection by the host system?

Reid: Yeah. Well, you have rejection and you have host-versus, graft-versus-host disease. But they had the regimens they finally used, I think, were fairly, and had fairly good results. I think they had about a 90 percent rate and I'm not sure, but it was in the nineties; it was very good. And we selected patients who, I think some of the patients' kids had had strokes, but if you, the theory was that if you selected patients before they had chronic disease, you'd probably do much better.

Williams: Okay, before they have it.

Reid: Yeah. Sullivan and Mark. Mark is out at Oakland. I don't know his last name.

Williams: Well, one of the things I'd like to track is just the community of researchers. Go back to the early ones. Who worked in their labs? Did they go on to become PIs on other things related to sickle cell? I just wonder if there would be a way to look at the different researchers and sort of track them. It may be complicated. I don't know enough now.

Reid: That's a big chunk.

Williams: Is that a big chunk?

Reid: Yeah.

Williams: Because one of the things that I was thinking is that, well, even if people didn't stay in sickle cell, they contributed to other fields because of the knowledge they gained in sickle cell.

Reid: I'm sure they did. They went on to something else.

Williams: Right. Even just like with Pauling, I mean, he was doing antigen antibody stuff before he got in there. So you could look at influences that made a difference in the sickle cell and other diseases. That might be interesting. But I'm not trying to make more work for myself.

Reid: What is the focus of your study?

Williams: Well, the thing is, once you ask a research question, you start to see other things, it's almost like you've seen with sickle cell.

Reid: All the other things that come up, too.

Williams: All the other things come up. But no, we don't want to lose focus from the primary study, which is this one.

Reid: And your primary one is going to try to track the chronology of basic research.

Williams: Basic research and clinical.

Reid: You're going to try to put the clinical in there?

Williams: Yeah.

Reid: That's nice.

Williams: And I want to pay attention to the fact that it influenced the progression,

so I am paying attention to things like funding patterns; I am paying attention to the social climate, all those things that may have had some influence. Or maybe they didn't but to at least to find out if they did. But it's to sort of get at this question of, will we understand a disease, what are some of the influences on how we go about developing treatments, largely looking at the basic and clinical. But like I said, there are also other pieces. It's never just purely the basic and clinical.

Reid: No, that's true. And I think you have a special issue with sickle cell because of its uniqueness, and I don't think anything else is comparable to that that I remember, that I know of right now.

Williams: Right.

Reid: I mean, I'm probably somewhat biased, but it is a unique disease, and it remains a public health problem.

Williams: Right. And I think that even if that comes out, I don't think people really can appreciate the uniqueness of sickle cell disease. I know I didn't until I started. And, you know, it gets at the very heart of our whole system. I mean, you have blood diseases. These things are very complicated. And I think our look at sickle cell has been a bit too simplistic because the mechanism seems so simplistic. We think the treatment necessarily has to be.

Reid: Right especially with all the things that we know.

Williams: Right. So I think it's almost an interesting sort of, yeah, I can give you a

simple . . . I can just change . . .

Reid: One of the areas you need to look at, and I don't know how -- I think they're pretty successful with the thing -- you can look at the fact that sickle cell disease is one that could not be studied in an animal model till recently.

Williams: Right.

Reid: And I don't know who. I'm trying to think who has the latest animal model.

Williams: I should know this. I did see the research on it.

Reid: Okay.

Williams: Well, you know, in *Science*, they were talking about these transgenic mice. Is that what you're thinking?

Reid: Yeah.

Williams: Yeah.

Reid: Somebody's come up with one more recently.

Williams: Right, I know.

Reid: I don't know whether in Alabama. I know all these people but forget their names. You can study a lot in vivo, which we could not do with the patients.

Williams: Right.

Reid: Answer a lot of the basic research questions.

Williams: Yeah, that's true.

Reid: If you have an animal model that you can really use to study the impact of drugs or certain components of the membrane or whatever, these are things that you can't do invasively in a patient. We've had nothing mimic the model, the human model before, and that's a lot of progress you can make.

Williams: That's true because they had to first create the disease model before they could even begin the treatments and maybe the recent paper where they found a cure for the transgenic mice.

Reid: Okay.

Williams: I should remember this, but I do remember some articles about this. But that's an important point that I think gets overlooked. But you're right. There are no sickle cell disease, natural sickle cell disease models . . .

Reid: That treated the patient.

Williams: Yeah, right. So that's necessarily going to complicate things. You know, I think that if I can bring out the subtleties, that I will have done my job. I mean, I think so because everything I've read seems to suggest that there's not been a good analysis of all the different components of it, and so people come to conclusions based on, almost like you said, sort of miscommunication or misunderstanding about it. And I think it's very easy for the public to say, "Well, if we knew this in 1949, what happened?" You know, it's purely a racial thing, it's purely a political thing, it's like you said, this is . . .

Reid: It's a major problem.

Williams: It's a major problem. There's no way to get around it.

Reid: Yeah.

Williams: So, we probably should stop with the trials, because that will help me . . .

Reid: If there's anything else you want from me, give me a call.

Williams: Okay.

Reid: Or an e-mail if there's something you want to clarify.

Williams: Well, once . . .

Reid: And write that other book, *The Real Truth*.

Williams: *The Real Truth*.