

Dr. Ernest Beutler

March 28, 2002

Today is Thursday, March 28. This is an interview between Dr. Valerie Williams of the NIH History Office and Dr. Ernest Beutler from the Scripps Institute.

Williams: Thank you for meeting with me today.

Beutler: My pleasure.

Williams: I have two tapes going so that in case one battery fails or one fails, we have backup. Why don't we get started. Maybe you could just tell me a little bit about how you got started in research. And I have your CV, so I'll refer to that, too.

Beutler: Well, I guess I became interested in red blood cells through my research with the Army malaria research project. I was stationed at the Joliet Penitentiary in 1953, when I entered the Army, and I started working on the question of why certain individuals, usually black, developed hemolytic anemia whenever they took the antimalarial drugs which we were investigating at that time, and that led to the discovery by myself and my colleagues of the G-6-PD deficiency, and I suppose that that's sort of the beginning of a lifelong interest in red blood cells and genetics. Most of the things that I've done in the laboratory over the last 50 years now really have been outgrowths of clinical experiences that I had. When I was on the house staff and on the junior faculty at the University of Chicago, I had patients with sickle cell disease, so I became interested in the disorder. I might say that Nixon's and Edward Kennedy saying that sickle cell is a neglected disease was really, I think, an untruth. It was not. It was really considered to be a prime disease for study. It was never a neglected disease -- maybe neglected by the politicians, but not neglected by the scientific community. So, and here was the first disease that was really

partially understood on the molecular level, and so since I was interested in biochemistry, interested in medicine, it as just a very attractive target.

Williams: Let me just back up a little bit-- I think one of the interesting parts of doing these interviews is to find out how people get into sickle cell. And you said that you were noticing that with the antimalarial treatment, you noticed hemolytic anemia from patients of African descent.

Beutler: Yeah, but that had nothing to do with sickle cell.

Williams: Right. But that sort of began . . .

Beutler: My interest in red blood cells.

Williams: I see, okay.

Beutler: Now that I think about it, I actually did some work that indirectly had to do with sickling at that time in that one of the burning questions at the time was, why had the sickled gene reached such high frequencies in Africa? And it was at that time that the malaria hypothesis was brought forward by Motulsky and by Allison. And I was in a situation where I actually could study this directly because I was working with human volunteers and infecting them with malaria. And so we actually did and published, I think, in the *British Medical Journal* or maybe *Lancet* -- I can't really remember, but I can give you the paper-- a study in which we infected people with sickle trait and those without sickle trait with *falciparum* malaria and showed that there really was no difference in the course of the disease, that sickle trait did not affect the disease. It was subsequently suggested that maybe the selective effect probably was malaria but that it only occurred or could only be seen in children or maybe in people who had some immunity because of previous experience with the parasite. So even in those days -- that was 1953 or '54 -- we were interested in the population genetics of sickle cell disease and sickle cell trait.

Williams: So at University of -- this was all at the University of Chicago.

Beutler: Yes. I was trained at the University of Chicago. I was an undergraduate medical student there, and then I was on the house staff. And when I was on the house staff, I had to go into the Army, and the University of Chicago operated this contract for the U.S. Army for the study of malaria, and that project was carried out at the Joliet Penitentiary. So I was then technically an Army officer, but I was working on a contract that was to the University of Chicago.

Williams: I see. So that experience sort of explains a lot. We talked a little bit about the research at the University of Chicago. Now, were there any other projects that you were working on?

Beutler: Well, the first project I worked on as a medical student in my first paper dealt with infection and the effect of radiation on immunity to infection, influenza virus. There were a few other things. But early on, I became interested in iron metabolism and in iron deficiency. And so one aspect of the work that I was doing during the '50s and early '60s was iron metabolism, iron deficiency, diagnosis of iron deficiency, biochemical effects of iron deficiency, and that sort of thing. The other aspect had to do with red cells, hemolytic anemia, and that probably fit the sickle cell disease interest a little bit more.

Williams: Okay, then. And who did you work with?

Beutler: Well, my main mentor was Leon O. Jacobson. While I was in the Army, the person who was in charge of that contract was Alf Alving, but actually, he was a renal vascular disease person and he really didn't know or understand much about what we were doing with this work. So, actually, my real mentor would have been Leon Jacobson, and he later became chairman of the Department of Medicine and dean at the University of Chicago, and he died just maybe four or five years ago.

Williams: Okay. So, how did the research that you conducted at the University of Chicago then relate to the work that you did when you were in California

at City of Hope?

Beutler:

Well, as you know, in academic institutions, you do what you want to do or what you get funded for, as the case may be, and although funding -- in the early days, funding was not really a problem for me because at the University of Chicago I was supported by a large grant from, I think, the Atomic Energy Foundation, the Atomic Energy Commission, I guess, to the University of Chicago. I was in the Argonne Cancer Research Hospital. So my mentor, then Jacobson, supported me. But basically I was able to work on whatever I wanted to, and what I wanted to work on in those days was our metabolism and sickle cell anemia and G-6-PD deficiency, and those are the things that I worked on. And, as a matter of fact, with respect to the focus on sickle cell anemia, which I guess is really the main thing you're interested in, my recollection is that I felt frustrated, as I think most physicians did, in our inability to treat a disease that we knew so much about. As I say, it was not a neglected disease; it was really kind of at the forefront of molecular medicine. But even though we knew there was an abnormal hemoglobin, we knew that when that hemoglobin was deoxygenated, the cells would sickle, and that this would cause painful crises, we just didn't know what to do about it. And in the late or maybe 1956 or '57, there was a very comprehensive review in *Progress in Hematology* and this was a review by John Harris in Cleveland, and in it, he rather extensively summarized the properties of the sickle hemoglobin, and I think it was from that paper that I got the idea that if I converted the sickle hemoglobin to methemoglobin, that this would impede, might impede sickling, because I think this article said that methemoglobin didn't sickle.

Williams:

Right.

Beutler:

And so I undertook studies at the University of Chicago in which I gave volunteer patients with sickle disease one of two methemoglobin-forming

drugs, either sodium nitrite or para-amino-proprionophenone, and induced methemoglobinemia and measured the red-cell life span with chromium 51. See, basically the experienced I'd had with studying G-6-PD deficiency carried over very well into studying sickle cell anemia because the issue was much the same, and that is the life span of the red blood cells and the metabolism of the cells in terms of methemoglobin formation and reduction. Then, when I moved to the City of Hope in December of 1959, I just continued those studies, of course, with different patients, and as a matter of fact, I'm sort of -- I'm somebody who doesn't really throw much of anything away, and over there we have a very large file room which has all my files, and I just had one of my secretaries pull out the two folders, one of the paper that I published on methemoglobinemia, and I still have most of the original drafts even though it's about 40 years old; and then there's a later one which we'll probably get to that I published in the *New England Journal*, which has to do with sickle screening, which might be of interest to you.

Williams: Well, I do -- actually, I have those papers.

Beutler: I bet you don't have the correspondence with the editors.

Williams: I have a lot.

Beutler: But not that.

Williams: Let's see. I do have your original one.

Beutler: Yes, that's right.

Williams: On methemoglobin. And this one that I . . .

Beutler: And there's something else in there, too, and that is that I proposed there -- and I think I was ready to first propose it -- that fetal hemoglobin would stop sickling, and then we did some experiments with chorionic gonadotropin, as you pointed out.

Williams: I did, and actually, this was one link that I'm not clear on, so maybe you could tell me a little bit about that, sort of the hormonal link there. You

talked about it here.

Beutler: Well, it had to do with an observation about the fetal hemoglobin levels of pregnant women, which was higher than non-pregnant women, and one might have thought that that might be due to trans-placental migration of fetal cells. But it had also been shown that women with null pregnancy, where there was no fetus, also had increased fetal hemoglobin levels, and that made me think that fetal hemoglobin concentration might be under hormonal control. We tried to develop an animal system for the study of the regulation of fetal hemoglobin about 1961 or '62. In fact, it's sort of interesting in retrospect. I submitted the paper to *Nature* about the regulation of fetal hemoglobin in the rat, and *Nature* refused it and said it was of no interest.

Williams: Really?

Beutler: Yeah.

Williams: Oh, I don't believe that.

Beutler: I don't know if I still have that or not.

Williams: Oh, that would be so interesting. Okay.

Beutler: Yeah. Well, I can look through the files and see if I still have it, but probably not. But we put a lot of work in. I'm sure I started a laboratory notebook I never throw those away. But there were hemoglobins that appeared in fetuses that then disappeared, and I thought this would be a very good way to try to study fetal hemoglobin regulation with the idea that this might help in sickle cell disease. Now, actually, we wouldn't have been able to get anywhere anyway because it turned out to be a much tougher problem than we thought it was. But I thought that giving the chorionic gonadotropin might do something to simulate the hormonal environment of pregnancy and increase fetal hemoglobin levels, and that's why I did it. I might say that I wouldn't have -- these days, of course, I wouldn't be able to do any of these things. We obviously didn't harm

anybody. We got useful information out of it. And yet now I think, even with chorionic gonadotropin, I guess I could have given it, but I would have had to jump through so many hoops that I think it probably just wouldn't have been worthwhile to do.

Williams: Right. I mean, that was one of the things I noticed here with the sodium nitrite administration, that there were some troubles with the patients in giving that. I sort of wonder, well, how were these studies approved? Was there a system of IRBs at that time?

Beutler: No.

Williams: No. Okay. These were landmark studies. I enjoyed reading through them. The meticulousness of the research, just the documentation, I thought it was incredible.

Beutler: Actually, I can show you. They asked me to cut it in half.

Williams: Really? I thought that this was really a very thorough study.

Beutler: Just this morning, in preparation for your coming by, I just pulled out a few things.

Williams: Oh, good.

Beutler: This is a picture which may or may not interest you. When I came to City of Hope, there was an organization in Los Angeles for Los Angeles Society for Sickle Cell Research or something of that sort, and they made a donation to my laboratory and I bought a small electric autoclave that I needed for some of my studies. And I was going through some of my pictures a few years ago and I saw I had this, and this is a guy awarding me the check. You know, it was \$300. So there was community support for sickle research in those days.

Williams: I'm sure there was.

Beutler: Here. I can give you a real reprint.

Williams: Oh, great. Okay. Well, this is so much better.

Beutler: A little yellow, but here it is. But I was just going through this and, see,

here is . . . If you're interested, I still have all the reviewers' comments.

Williams: Oh, I definitely am.

Beutler: These are the original figures. But this is not -- I think this was the first one, I think, in March, and these were their criticisms, I guess.

Williams: Oh, really?

Beutler: Yeah. See, these are the . . .

Williams: Oh, I would love to see that. That would be excellent. This is great.

Beutler: I can give you all of this.

Williams: Okay.

Beutler: And then this is . . . Apparently I wanted to present this at the Western Society, but they didn't put it on the program, didn't think it was very interesting.

Williams: Oh, really?

Beutler: But if you'd like, I can have my staff copy those things for you.

Williams: I actually would. I've been trying to really document the research, all the different avenues and paths people tried, how early they began to formulate hypotheses about different things, because I certainly had the information about Janet Watson in 1948 sort of suggesting the link with fetal hemoglobin.

Beutler: Yes.

Williams: And then I wasn't sure exactly where that went afterwards. It's interesting.

Beutler: Well, it didn't, I mean, it was sort of . . . I think she noticed it, that there was a time before the sickling occurred and thought that sickle hemoglobin interfered. I have her paper, her 1948 paper.

Williams: It was 1948, wasn't it?

Beutler: What I do remember having heard in the '50s -- I never knew Janet Watson, but what I'd heard is that she had done chromatographic studies on hemoglobin and that she had thought there was an abnormal

hemoglobin in sickle cell disease, that she discovered that before Pauling did, but that she had never published it because she wasn't sure.

Williams: Well, right. He clearly established it.

Beutler: Well, he had a Tiselius apparatus and she had a piece of filter paper. I guess that was the difference.

Williams: That was the technology. Technology made all the difference.

Beutler: Yeah.

Williams: That's another piece that I'd actually like to follow in terms of the role that technology played in the development of treatments. But this is classic, and certainly if copies of these could be made, I'd love to keep them for the files because, like I said, a lot of the story just hasn't been put together. I mean, there obviously is the chapter in *Blood*. It sort of goes over it, but it's a little bit personal. It's more of a personal story, and I really wanted to follow the scientific progression of knowledge.

Beutler: Yeah. Let me get them to copy this.

Williams: Oh, that would be great.

Beutler: If you're interested in that graph of mouse and ...hemoglobin, I'll dig for that.

Williams: Okay, okay, great. I didn't even bring all of the papers that I had. I think there was a letter from James Neel that referenced the ones that you've done. I have to find that. And it talked about, I think, some of the carbon monoxide.

Beutler: Yeah. That was later.

Williams: We'll get to that. But just to clarify, it's in the paper, but just for the sake of the interview, your primary hypothesis at this time about methemoglobin was . . .

Beutler: Well, it was basically this: that the methemoglobin containing red cells would not sickle. We, of course, realized that you couldn't convert all the hemoglobin in methemoglobin. There'd be no oxygen transport. But the

idea that I had was that if I could introduce into cells some methemoglobin molecules, that that might interfere with the aggregation of the molecules, you see. So it was basically that the methemoglobin would prevent the sickle hemoglobin, the produced sickle hemoglobin, from reaching sufficient concentration.

Williams: Right.

Beutler: I have some slides that I showed in presentations in 1959 or 1960 showing that schematically.

Williams: Really?

Beutler: Yeah.

Williams: Oh, I would love to see it.

Beutler: I never throw anything away.

Williams: Well, aren't you a goldmine! I'm so happy to hear that because I've been limited in terms of some of the artifacts, and all these little pieces would help. There was also the idea of inhibiting the polymerization, and this is some of the work that Murayama did. So how did your hypothesis and your way of thinking about inhibiting sickling sort of play into some of the other ideas?

Beutler: Well, let's see. Murayama got Nalbandian started on urea. Right? But that was considerably later and it was very different, and also was not very well documented. I mean, that was, as I'm sure you know, very badly received, and for very good reasons. No. I thought our work was well received. I mean, you'll see that people raise questions published in the JCI, which was at that time really the premier clinical research journal, and I was always well funded. So that's one reason why I really take strong objection to the idea that no sickle work was done and that no money was spent, because when I presented proposals, they were funded.

Williams: Okay. So now I need to understand a little bit about how your research on methemoglobin connected to the work you did a little bit later with 2,3

diphosphoglycerate, I think, which is sort of the next big . . . This was actually -- Charache did a paper earlier, I think one year earlier than you did, but it was very similar in terms of -- I didn't read his as thoroughly as yours -- but on the sickling phenomenon. So maybe you could bridge that gap in terms of the research studies going on.

Beutler: I'd sort of forgotten about that. Actually, Sam liked my formulation. I was rather pleased. He -- I can't remember exactly what he did, but I know we had a talk about it once and he told me that he thought that . . . I guess that he hadn't understood it the way that I formulated it at the time that he was working on it. And basically, I think my formulation was based on Perutz's model of the allosteric nature of the hemoglobin molecule, and it became apparent to me that 2,3 DPG would stabilize the deoxy conformation and that that would be a very bad thing, and that if one could deplete cells of 2,3 DPG, that would be a very good thing.

Williams: Okay. And at this point had you put the methemoglobin story to rest?

Beutler: Yes. I think the way -- my feeling about methemoglobin then, and now for that matter, is that it works, but it's not practical, that if one could maintain a steady state of 10 or 15 percent methemoglobin, that might very well be beneficial in sickle cell disease. But how would you do it? And so, of course, I would have to say that drug administration and pharmacology has moved a long way in the last 40 years, and maybe the idea is worth revisiting, but I would say that in the context of the time, it, after establishing the principle, it became apparent that the boundaries of what was safe were narrow enough that one couldn't really reach them in a clinical situation. One could in a clinical research situation, and we never harmed anyone, but I would not have dreamed about sending somebody out with a bunch of para-aminopropiophenone and saying, "Take this." So I just thought it wasn't practical enough.

Williams: Okay. And just remind me, what were the side effects of sodium nitrite?

Beutler: Well, the para-aminopropiophenone actually had relatively few side effects on the patient, but it proved to be somewhat hemolytic, so that

what we found was, as I recall from the paper, is that initially it increased the life span of the red cells, but then they went down, which I figured was really the hemolytic drug. And sodium nitrite is not hemolytic but it produces very bad headaches in some people, and arrhythmias, too. But the headaches...I remember quite vividly being very concerned about one of my patients at City of Hope because she got a very bad headache, and I was concerned that something really bad was going to happen, but it didn't and this is known. If you look in the pharmacology book, nitrite produces vasodilation that can produce headache.

Williams: Okay. So we put the methemoglobin story to rest when you sort of moved to the 2, 3 DPG studies.

Beutler: Well, 2, 3 DPG was much later, I think 10 years later perhaps.

Williams: Yeah. It was '71, so you're correct. So I guess I'd have to look at your records, but in between that time period, am I missing something?

Beutler: I don't think so. Carbon monoxide was even later.

Williams: Right, that's later, and I have some of that as well. That's an interesting point because one of the things that I realized, particularly with Harris's paper, was the body of knowledge that existed before Pauling. I mean, not to take anything away from Pauling's paper in *Science*, but there was a lot of -- there was a body of research that existed that all but said that there were two hemoglobins.

Beutler: Oh, you know, I'll tell you, I don't give Pauling much credit with this. I mean, basically, it had been shown that stroma didn't sickle, and the assumption was it was the hemoglobin. And he happened to have the machine that could look at the hemoglobin.

Williams: Exactly.

Beutler: I mean, I don't think it was as if he had some great insight. He just had the instrument that other people didn't have.

Williams: He did, and I don't know if I have this with me, but one of the other things

I documented -- and this is really based on, again, Harris's work because he did this, he put this together in his paper in 1959. I'll have to see if I actually have it with me, if I remembered to bring it. Perhaps I didn't. But I have a list of all the properties, the physical chemical properties that were known by 1949, just prior to Pauling, so it's like you said, he more or less clearly demonstrated what many had alluded to or at least, had they had the proper technology, would have been able to show.

Beutler: And the fact is that Pauling didn't win his Nobel Prize for sickle hemoglobin. He won it for the nature of the chemical bond.

Williams: Exactly.

Beutler: Which I think was probably appropriate. But I think that his contribution to sickle cell was relatively minor in that sense. Maybe minor is putting it too strongly, but I don't think this was a huge breakthrough and nobody had understood it and suddenly he did.

Williams: Right, right, and suddenly he did and I think that's one of the points that I'd like to bring out in this snapshot that I give from '49 to '70, is that, as you said, the role of technology was more important in sort of putting Pauling in the place in history that he had.

Beutler: Yeah, because in 1949, who had a Tiselius apparatus?

Williams: Right.

Beutler: It must have been just a handful around the country.

Williams: Yeah. And they were very big apparatus.

Beutler: Oh, it was a whole room.

Williams: It was a whole room, right. It's so amazing. I mean, you think now about gel electrophoresis and . . .

Beutler: Yeah. And that wasn't that long in coming. In fact, I suppose that one could even make the point that maybe the demonstration that sickle hemoglobin has a different charge must have been incentive to people to try to develop better electrophoretic systems. So, for example, people like

Motulsky developed electrophoresis at that time. Is Motulsky one of the people you're going to talk with?

Williams: I'm going to try. He's certainly on my list for that time period.

Beutler: Yeah. And he worked, see, he worked with Singer, not John Singer here but . . .

Williams: The two Singers.

Beutler: The Singer [Karl] in Chicago, who died rather young, who did the basic work on fetal hemoglobin back in the early '50s and found it was increased in thalassemia and so forth. So Arno was very much in this field. So after Pauling's work, it became apparent that electrophoresis was going to be something important to do if you're going to understand human disease, and the hemoglobins were a very important target, but also, of course, the plasma proteins and so forth, so I think it helped to carry the whole field of biochemical medicine along.

Williams: Right. I think that's a story that needs to be sort of told and brought to light, and that's, I guess, one of my goals in doing this type of study, to put some things in perspective, so to speak. One more question just about your research here. So the funding that you received for most of your research? I know that the Atomic Energy Commission funded...

Beutler: Well, that was when I was at the University of Chicago. Now, when I moved to the City of Hope, of course, I didn't have any grants, and then I applied for a grant that was entitled, *Formation and Survival of Red Blood Cells*. And the first time that I put it in, it didn't get funded. It was deferred. I think they wanted to know how much support I was getting from the City of Hope. But then the next time around, it was funded, and it has been funded since 1961 continually.

Williams: Really?

Beutler: Yeah. And I actually didn't apply for renewal this time because my work has moved so much in the direction of iron now that I just was not too

interested in carrying that forward, although it's still -- I still can apply. In fact, I was thinking -- sometimes I get ideas that maybe I will put it in. So, actually, I've been funded by the NIH for over 40 years for red-cell studies, and the sickle cell work was part of that. I never had a separate grant to study sickle cell disease. In fact, I think this may be one of the reasons why people who have written articles that I consider to be quite inaccurate about the lack of funding for sickle cell disease never really appreciated the fact that a lot of money was being spent by the NIH for sickling. I know there was an article by this guy, whose name I've forgotten, how much more money has been spent for cystic fibrosis than for sickle cell disease. Well, I don't think that was ever true, but I never really did the work to find out. But I know that my project would very likely not have been considered a sickle project, although it wasn't all, but all the work I did on sickling was supported by that grant.

Williams: Okay. So you're thinking that maybe, because this is another interesting avenue to follow, which is the funding, that if you just looked for funding that was based on sickle cell in the title or something like that, it might seem to be a relatively small number compared to other diseases. But if you broaden, for example, your scope to look at some other things, you might see more.

Beutler: Well, yes, and there are two ways of doing that. I mean, one is to say, well, in my case the sickle cell work was all in there. It was actually clinical work on sickle cell disease. The other is that somebody may have been working on how to clone genes, and that wouldn't appear to be work on sickle cell disease, but obviously it would have some real application. And as a matter of fact, I'm sure you're aware of the fact that the first paper on PCR was on the detection and mutation in sickle cell disease.

Williams: Right. And that's another point that I'll want to get back to but just to follow the research, so the effect of DPG was sort of at the beginning of

the '70s...I don't know if I went through this paper as much.

Beutler: Which one is this?

Williams: Oh, I went to the next one.

Beutler: Is that where we did the falling ball viscometer?

Williams: No. That's the next one. Actually, this is the one that I was more familiar with. I've never seen this falling ball viscometer. I'd love to see just what that looks like. I'm sure it's not that elaborate.

Beutler: No, it isn't.

Williams: It would be interesting to see.

Beutler: Well, I don't have it anymore.

Williams: You don't have it.

Beutler: I did this work, when, '73 or . . .

Williams: Seventy-two.

Beutler: People in the lab, they throw away stuff after 30 or 40 years, you know.

Williams: That's too bad.

Beutler: But I can tell you what it looked like. It's just a glass tube and a bb.

Williams: Really?

Beutler: Yeah, like a bb. It's just a ball. And my recollection is that the ball might be, let's say, three or four millimeters in diameter, and I think I used ligroine. Did I?

Williams: You used ligroine. That's right.

Beutler: And so we would fill the, we would do whatever we want to do with the hemoglobin. We would fill the tube with the hemoglobin, cap it with ligroine so that it wouldn't get oxygenated, and then we would drop the ball through it and see how long it took for the ball to drop through it. And, of course, when hemoglobin aggregated, the viscosity was higher and the ball would fall very slowly, and go faster.

Williams: So was it a function of the speed or the distance? The time that it took or how far down?

Beutler: No. I think we always let it drop to the bottom.

Williams: So it really was the time.

Beutler: A hundred millimeter. That's right, so a distance on the tube. I guess you wouldn't necessarily have to go to the bottom, but it was most of the tube.

Williams: Okay.

Beutler: We started the stopwatch when it hit this point and hit it again when it got to that point, and that's how long it took.

Williams: I see, maybe you can just put some of these studies in perspective.

Beutler: Well, I thought we were going to-- if we're going to try to screen for agents that might stop sickling, that you had to have a system, and there wasn't really a very good one at that time. That was really basically it. I had done a lot of work-- some of which was reported, as a matter of fact, in the paper you like on methemoglobin -- on what percentage of cells sickle in a certain time. But that's a very semi-quantitative thing, and I thought if we had a system where we could really check and see in numbers rather than counting the percentage of cells that were sickled, because if you looked at sickle cells, some are a little sickled, some a little more sickled, and so forth, so that's really basically why we did it. We never really pursued that much further. I think we tried a number of different compounds like acetyl salicylic acid. That didn't work.

Williams: Right.

Beutler: I haven't looked at this paper for a long time, so it wouldn't be . . . These would be desaturated, then it moved very slowly, but if we looked at acetyl salicylic acid had virtually no effect. If we did urea, it had very little effect, too. Actually very little effect up to 500 millimole, I think that was.

Williams: Right, okay. That's the point that you and Murayama factor essential for the sickling process.

Beutler: Yeah. We added boiled extracts and it didn't have any effect. So I think

what I suggested was this could be useful, and I don't know to what extent it was picked up by other people, whether people did or not. I don't think there was much done with it.

Williams: No. I didn't see too much. I have to do some more searches, but I was very interested in this technique, again, looking at the role of technology and some of the early ones that were used.

Beutler: Nowadays, of course, high-throughput chemistry is all the rage. Now, maybe this isn't ideal for that, although it's entirely possible that somebody could do something like it to measure viscosity and that one could start looking at libraries of chemical compounds to see which ones affect the viscosity, and then you build on those. So it was just that kind of approach.

Williams: I see.

Beutler: But I never took it anywhere.

Williams: Okay. That's very interesting, though. Let's just keep going. I want to get to carbon monoxide. Now we're dealing -- this was the whole body of research on the dissociation curves and the right and the left disassociation curves, and this started another, I would say -- this is '74 -- started another segment of your research. Maybe you want to tell me a little bit about that.

Beutler: Yeah. That's what I think -- this was based on the model now that has been made by Max Perutz, you know, the allosteric properties and the tense and relaxed form of hemoglobin. There's another part of my scientific life that basically this was perhaps related to, and that is that one of the major areas that I worked on in the early '70s and even a little later. I was red-cell preservation, and as you probably know . . . Well, maybe you don't, but let me give you a little history of that. For many years, the name of the game in red-cell preservation was to try to find storage conditions, which would allow red cells to be stored outside the body for

many weeks. Okay? And the limit was about three weeks in ACD, acid citric dextrose. The introduction in the '60s of a solution called CPD extended that to about 28 days or four weeks and then the introduction of adenine. This was sort of exploited by Ernie Simon and extended to 35 or 42 days. The field then sort of leveled off. People kept doing the same thing again and again as people do in some fields. And then there was, to me, a rather startling discovery, and, again, the information, much of the information had already been in the literature, but nobody had really paid attention to it until Janet and -- I'm blank on the name right now; it was a husband-and-wife team at Columbia Presbyterian, I think. In fact, Frank started a postdoc with him. But they discovered that when you stored red cells under these conditions, that they had a very high oxygen affinity.

Williams: Okay.

Beutler: Actually, it's not really too important and I can look it up. But the discovery was that if you stored red cells for three weeks, let's say, and their viability was very good, that if you measured the oxygen dissociation curve of those cells, it was far-left shifted, and that turned out to be due to the fact that the 2, 3 DPG had become exhausted. And the 2,3 DPG had nothing to do with the viability of these cells, that is, their ability to survive in the circulation. And as a matter of fact, we showed, using the differential equation method, that the 2, 3 DPG was regenerated within about eight to 24 hours after the infusion. But if you transfused a patient who really needed oxygen-carrying capacity in a big way, that might not be soon enough. And I might just digress for a moment. The way that we showed the regeneration is that we stored some blood for several weeks, and it was type O blood, and then we transfused that into type A patients. We glutinated out their A cells and were able to measure the regeneration of the 2, 3 DPG and the O cells . . .

Beutler: I'm in the process of having almost all the interesting reprints I have

scanned and put into PDF files.

Williams: Oh, isn't that smart.

Beutler: So I've got them all on my computer files. Here, let me get this in order, and then I'll show you what I think is really particularly charming. The whole thing is really interesting. Read this letter that she wrote in 1972 to Dr. Fairbanks.

Williams: Okay.

Beutler: It's kind of moving, isn't it?

Williams: It really is. That is special, I spent a good deal of my time doing research, at the Mayo Foundation.

Beutler: It is an interesting story.

Williams: I'm glad you shared this.

Beutler: So, to get back to our main thrust, I was interested, therefore, in 2,3 DPG and 2,3 DPG metabolism, initially not because of any relationship to sickle disease, but because of the relationship to blood preservation, you see. So I became reasonably knowledgeable in the measurement of 2,3 DPG and how it was regulated and so forth, and I gave a lot of thought to the idea that one might be able to help patients with sickle cell disease by lowering the 2,3 DPG level. But I never really was successful in thinking of a good strategy, so I never pursued it, and I don't think anybody else really has either. You see, the most obvious way to deplete 2,3 DPG is by inducing acidosis, but acidosis itself produces [?] in the hemoglobin molecule, so that would be very counterproductive. And the enzyme that breaks down 2,3 DPG, 2,3 DPG phosphatase, is very strongly stimulated by thioglycolate about 3,000-fold. So if one could increase thioglycolate levels in red cells, that might be the way to approach the problem. I don't know if I ever published that anywhere. I couldn't think of a way to do that. As a matter of fact if you look at some of the other publications, which you probably didn't notice because they're not related to sickle cell

disease, about 20 years ago, we started to look at how thioglycolate was made in red cells, but that didn't give us any clues on how to approach it. So those papers, which are in my bibliography, really don't seem to have anything to do with sickling. In a way, it's a good example of the fact that you can't look at NIH funding or projects and really know what the relationship is.

Williams: Right. And that's another thread that I hope to pick up on, because this question of funding is so key to the perception that there's not been a focus on the disease, and so in that sense I think you're right. If you can track down the funding and get at it in other ways other than a keyword search or just the grants that went for the sickle cell disease program, for example.

Beutler: Yeah. I have sort of an iconoclastic theory about the relationship between funding and research output. And since you're a physical chemist, it is analogous to substrate....

Williams: Okay.

Beutler: But I think of it as expenditure against product. If you have no expenditure, then you have no product. As you increase expenditure, you increase your product, and then you go back down.

Williams: Interesting.

Beutler: That's a theory and product inhibition as applied to research funding.

Williams: I would say it would just plateau, but you're saying it goes down.

Beutler: The reason it goes down -- this is my theory -- is that as you put more and more money into it, you begin to attract all the people who failed to get funded for anything else. Now, those people do crappy work, and then they overload the literature with unreliable findings that begin to confuse the field. So now people who could be doing good work are misled into doing things that turn out not good.

Williams: Or pulling out, as it were, just because, like you said, the field has become

so overburdened with a certain caliber of researchers.

Beutler: Yeah. Well, that could be, for example, in the field of sickling, take the urea story, for example. Now, if that had never happened, probably the field would have moved along faster because a whole bunch of people who started working on urea and then cyanate and so forth, and actually, that was a blind alley. And if that work hadn't been done, they might have missed something really important.

Williams: That's an interesting way to think about that, so that's a good point. So hence the downward shift.

Beutler: Right.

Williams: Okay, then. Well, let's just keep going because I have other questions other than just your research, but this was sort of where I wanted to start. So now we're in carbon monoxide. This is '75.

Beutler: Carbon monoxide is -- it's really back to the methemoglobin story.

Williams: I thought so.

Beutler: It's really the same thing, but I thought it would be more controllable, and it is more controllable, because while the red cell can reduce methemoglobin quite rapidly, particularly young red cells, the dissociation of carbon monoxide from carboxyhemoglobin is relatively slow. So if you give somebody CO every four hours or so, you know . . . In fact, it occurred to me as I was fantasizing about this over those years that maybe people with sickling need to smoke more, and then they would get carbon monoxide. I might say I did think about that, but it also made me think that it might not work because I was sure that there were a lot of sicklers who smoked, and that I'd never heard a sickler tell me, "You know, doc, when I smoke, my symptoms get better." So, anyway, my thought was just that this was a more stable way to form a liganded binding derivative that was in the oxy conformation.

Williams: Right. And it really, as you said, goes back to the basic hypothesis of the

methemoglobin studies.

Beutler: Right, to change the hemoglobin molecule. And I think that the strength of the idea then and now is that you don't have to do it with very many of the hemoglobin molecules, that if you could convert 10 percent of the molecules into non-interacting molecules, it would probably have a very beneficial effect.

Williams: Sure, right, right. Let's see. Was there anything here that I wanted to cover with the carbon monoxide? Was this one of the first studies? Did you have therapeutic trials, like clinical trials, in this instance? Studies? Was this the first set?

Beutler: Methemoglobin was a clinical trial, too.

Williams: Yeah. I guess I was thinking more formal, with the four formal IRB review process.

Beutler: I don't know if we had IRBs then or not.

Williams: Okay. I was trying to track...

Beutler: Yeah. I can't remember when that happened. It may have been . . . I really don't know.

Williams: Okay. That was just another piece of it.

Beutler: It might have been, but I certainly was aware of the fact that carbon monoxide was toxic just like nitrite is toxic, too. But I did some rather extensive reading on how much could be tolerated, and also what I did was I didn't have 100 percent carbon monoxide. It was a relatively low concentration. What did I use? I can't remember.

Williams: The whole thing about the smokers-- containing 20 percent carbon monoxide. Okay. Unwittingly administered 20 percent.

Beutler: It went to a mixing valve, you see, and what I did was to use a concentration which had been shown in studies to level off at a fairly safe level.

Williams: I see. Okay, then.

Beutler: You see, smokers will sometimes have as much as 20 percent carboxy hemoglobin in their blood, so it's not as if people . . . And people in cities who work in [unintelligible], so forth have carboxy hemoglobin. But you don't want to get up to 40 or 50 percent because that can be very, very toxic.

Williams: Okay. Now, one of the things that just sort of occurred to me, how did you manage to do all of this research as a physician? I mean, now when you think about physician researchers, people talk about that essentially being a dying breed, that physicians essentially have very little time to conduct research.

Beutler: Well, there's a lot of reasons. I like to tell my female colleagues that what they need is a good wife. You've heard that expression.

Williams: Yes, I have.

Beutler: So, you know, I mean, there are a lot of factors, and I'll be glad to tell you all of them. One is that I was always willing to work very hard. And there are a lot of people who say that something can't be done, but they don't want to work more than 40 or 50 hours a week, and I always normally had a 60- or 70-hour work week. So that's one thing. A second thing is that, although I have a very nice family, my wife stopped working when we started having children and she raised the children, and I was there some of the time, but we didn't have the ethic that I took 50 percent of all the household responsibilities and she took 50 percent. That certainly made it easier. But there's something else, too, and that is that I never spent more than probably about 20 percent of my time as [unintelligible]. I've always been very strongly laboratory based. See, I became chairman of the Department of Medicine at the City of Hope at the end of 1959. Before that, I was on the faculty of the University of Chicago. In either instance, but certainly when I was on the faculty of, when I was chairman at City of Hope and when I was chairman here, I had people who could cover for

me. So it's not as if I had a practice going and that I had to see patients half a day every day and. In fact, I think that people who do that will never really accomplish anything. I was always very close to my laboratory, and I trained all my own people. And there's an attitude that some physicians who go into, think they go into research have, and that is, well, if I want chemistry, I'm going to hire myself a chemist, and if I want to do some animal work; I'll hire myself a biologist or I'll get somebody to do that, and I'll come in on Friday afternoons and I'll encourage them and see how they've done.

Williams: Exactly.

Beutler: Well, from very early time on, from the time I went to the City of Hope, well, even before that, at the University of Chicago, Leon Jacobson, who was my mentor, was kind enough to supply me with two full-time technicians. I started working in the laboratory when I was a medical student, as a matter of fact, and I worked on influenza virus infection. I don't work in a laboratory now or just do very dull things, but I've had many, many years of hands-on laboratory experience. I'm quite proficient in the laboratory. Since 1959, sort of a steady state, I always had five technicians that reported directly to me, whom I trained, and a few postdoctoral fellows. It's sort of the reverse, as I'm sure you realize, of the usual model. I don't depend on postdoctoral fellows. I depend on technicians.

Williams: You don't have these warehouses of postdocs.

Beutler: Right now I have one postdoc and never had more than three. But until the last few years, I've always had about five technicians, and they're usually the same five. And the reason I don't have quite that many anymore is I retired.

Williams: Really?

Beutler: Yeah. So I just have two technicians that directly report to me now. One

of them is Carol West, and she's been with me about 34 years. And the other one is much younger, and that's Terri Gelbert, and she's been with me for 22 years now. And then I had people who'd been with me for between 18 and 25 years who retired in the last few years because they or their husbands got to the age where they want to retire. So that's the model that I follow. I think I was a reasonably good. I stopped seeing patients when I turned 70.

Williams: Oh, really?

Beutler: But until then, I saw patients. If I saw a new patient, for example, I would always have a clinical fellow do the history and write up the case and write the letters and so forth, and I would go in and see, I would listen to him talk to him about the case, go in and see the patient, and that would take me a few hours a week to do.

Williams: Really?

Beutler: Yeah.

Williams: Okay, then. That's not a model that exists today in any aspect of what you said, I mean, even from the point of training postdocs to being able to divide your time.

Beutler: Yeah. Well, there's been a real split. I mean, the people who were my role models did this sort of thing: Leon Jacobson, who was a very prominent scientist who really did most of the basic work on radiation biology, and he was a member of the National Academy of Sciences and he was a very prominent scientist, but he saw patients. There are some, still, but they are not the younger ones usually. For example, I'm sure you know Frank Bunn. Frank still sees patients but he's a very good scientist. Now, my own children, three of the four are physicians, and one of them is a professor here at Scripps, and he's really quite a famous scientist. He's really very, very successful. He is an M.D. but he never wants to see a patient again. He hasn't seen a patient in 10 years.

Williams: Really?

Beutler: Two of the other children are pure clinicians, and in a way, that's the way of the time. I don't have anybody who does both.

Williams: Right. I don't think that exists very much now, people who can do both. And I think you're right. If they do both, they probably aren't able to do either one very well, because to do research is extremely time-consuming. To pioneer a field, in particular, is extremely time-consuming.

Beutler: But, you see, I have been very fortunate because I was fairly successful very early on in my career. See, I was only 21 when I graduated from medical school, and when I was 31, I was chairman of a department. And that gave me a command of resources, and when I say resources, I don't mean research money, but I had secretaries, I had technicians. So I really had people who could help me. They didn't have to do everything themselves. And there's a lot of luck involved in research, and if you don't have some luck early on, then it's very bad because then you don't have a secretary or you share a secretary with three other people, and then you really can't move forward.

Williams: Right. You really reach a point where all you're doing is trying to stop from pedaling backwards. Do you know? I mean, that's where you are.

Beutler: Yeah. One of the stories I like is about, probably apocryphal, about the question that Napoleon Bonaparte asked applicants for the job of general, and he asked them only one question, and that was, "Are you lucky?"

Williams: Really?

Beutler: Well, I don't know if that's true or not, but I think it that being lucky is very important, and I think I was lucky early in my career, and that it doesn't help much to be lucky at the end of your career.

Williams: No. You're right. There's a critical period where luck can almost vault you, somersault you, to a whole other place.

Beutler: Right. And so if I hadn't had that good fortune, then I would not have

been able to continue seeing patients and doing research, but I could because I had the people to help me.

Williams: Okay, okay, then. That was a little bit of a diversion, but what I want to talk about now, then, is to get a big-picture view, and I guess my first question is, so in your mind, how would you characterize the sickle cell disease research in the '60s? If you could think about it in sort of a very broad lens or scope, how would you characterize that?

Beutler: Well, I think it was one of the big intellectual challenges in hematology and it attracted some of the best people.

Williams: Mm-hmm, okay.

Beutler: Fifties and '60s.

Williams: Fifties and '60s.

Beutler: Yeah, '50s and '60s.

Williams: I would agree with that. I find it hard to sort of separate those two periods. The '70s introduces a whole other element.

Beutler: Yeah, right. But we talked about some, John Harris, you know, Frank Bunn, who's getting started, Helen Ranney. I mean, these were world-class quality scientists, physician scientists, and that was because it was an important disease and it was an intellectual challenge, I think, that attracted the best people.

Williams: It attracted the best people. We talked about the key research questions as well as the key researchers. But kind of going back, was there a lot of interaction between basic and clinical researchers during that time period, or did people think about that divide in terms of, are you a basic researcher versus a clinical researcher?

Beutler: I don't think so. I think most of the people that I think of as having been important in that period are people who were M.D.'s and who saw patients, I think all the ones we named, and I can name some more. Frank Bunn, Helen Ranney, Ernie Helinx [sp.] in England, okay, Arno Motulsky

in this country, Tony Allison, even Harvey [unintelligible] who was a pathologist.

Williams: Right, that's true.

Beutler: Well, you read John Harris's papers. This was not some clinician bumbling around.

Williams: Right. Do you have this correspondence? This is from the 17th Congress. You probably have this, about your idea here about the left-shifted. This is from *Lancet* in 1978.

Beutler: Did I write this?

Williams: No.

Beutler: I don't remember this.

Williams: It references you.

Beutler: Well, I think this is . . . Well, I didn't argue a left-shift association, I argued for hemoglobin in the oxy conformation. That's not the same thing, I think.

Williams: Okay.

Beutler: Yeah. I don't remember that.

Williams: Oh, you don't?

Beutler: I did phosphate, too. I don't know if I ever did aspirin. Aspirin was -- I thought aspirin would be terrific because when I was out in the hematology study section in the early '70s, people became interested in the fact that aspirin acetylated platelet proteins, and I thought, well, maybe it's going to acetylate hemoglobin. And so I think I did some trials on aspirin, but nothing came of it.

Williams: Yeah. There's always the question, just as I think about it, of selectivity. I mean, getting things to modify at the site that you want them to.

Beutler: That's right. On the other hand, as we said, with sickling, if you modify a small percentage, it might be helpful, and if the agent itself is very benign, like aspirin or phosphate, then you don't pay much of a price for its

modification.

Williams: Right. That's true.

Beutler: Yeah. I think we may have published the phosphate studies.

Williams: Okay. Because that was the reason why I pulled that one out, because that was a study that, again, I didn't see.

Beutler: Yeah. We did that.

Williams: That was *J. Biochem. Med.*, so I think I have that.

Beutler: Yeah. See, this technician is still with me.

Williams: Oh, Carol West. That's the one you want.

Beutler: Yeah.

Williams: Really? Okay, then. So we talked about the '60s and we even touched on the funding, so I'm not going to ask.

Beutler: There's one other thing that happened. I pulled out the article because I thought it was interesting, and I don't know if you've seen this or not, but when I was on the hematology study section, I became concerned about what I called the hazards of screening, and I've got some very original drafts of that.

Williams: Oh, wow, okay.

Beutler: See, even when cutting and pasting meant that you actually . . .

Williams: Cut and paste. Oh, that is something.

Beutler: So, there's an interesting footnote to that, and that is that most of the members -- I have letters here from all of the members of the study section signatures, with one exception, and that was Helen Ranney. She didn't want to sign.

Williams: Really?

Beutler: Yeah. I think that Helen Ranney at that time was more concerned perhaps about political correctness than I was, but . . .

Williams: Okay. Well, right. She may have been at a different stage. Maybe . . . Were you at this point pretty well established to come out on this?

Beutler: Yeah, but she was, too.

Williams: She was?

Beutler: Oh, yeah. She was very well established.

Williams: Right.

Beutler: But she was involved . . . Well, you can read her letter.

Williams: Right.

Beutler: See, I thought that was an impractical approach and that just to say that being positive about education didn't really address the issue as I saw it. I remember being called a racist by some geneticist in New York when this was discussed.

Williams: Really?

Beutler: Yeah. There were some people who were very upset about this because, as Helen points out, people were very gung-ho about screening, but I saw some very bad things happening.

Williams: Arta Motulsky Well. That's a good segue into the '70s because, as I look at this, there are a couple of layers. There is the basic science progression, and that's one thing that I'm going to chart. Then there is the sociopolitical aspect of the whole thing, and that starts with the '70s, with this whole idea about the screening and programs and education and getting community involvement, political advocacy. So maybe you could tell me a little bit about some of the controversies about the screening debate. I mean, I have some of that information, but just . . .

Beutler: Yeah. Well, I think I really basically said I was very concerned, and I -- at that time I was in the Los Angeles area. Darlene Powers, whom you probably know, was very interested in sickling at that time, and I heard from her about some pretty bad things; for example, people well past the age of childbearing being screened and being very frightened. And people were very confused about sickle trait versus sickle disease. As a matter of fact, I had a clinical fellow with me who did a very nice survey, which I

think we published in the *JMA*, Dale Kellon.

Williams: Paul Kellon. Spell the last name.

Beutler: K-e-l-l-o-n.

Williams: Okay, Dale Kellon.

Beutler: And we did the survey, and it's published in the *JMA* and it wasn't all one way or the other, but there were lot of people who really didn't quite understand the difference. A survey of physicians. Physicians didn't understand the difference between sickle trait and disease.

Williams: And the disease. Isn't that interesting.

Beutler: It was a very -- it was relatively common for people to think that sickle trait was a mild form of the disease.

Williams: Right, and under certain conditions it could escalate to the disease.

Beutler: Yes. Or that it was just a mild form of the disease. For example, I remember I wrote one letter to *JMA* which was published, answering the inquiry where I think the idea was that if somebody had sickle trait, they would be a little anemic and they'd maybe have a little pain and so forth, and that's really pernicious thinking because then you overlook the real cause of anemia. If you think that you found out a patient has sickle trait, you don't have to worry that their hemoglobin is only 10, well, that's really pretty poor.

Williams: Exactly.

Beutler: And I think it's the analogy with the thalassemia trait that deceived some physicians, and that is that the thalassemia trait, of course, people are a little bit anemic. But in sickle trait, they're not, and you have to make that distinction.

Williams: Right, that's an important point. So in thinking about the '70s, what affect do you think that the national program or the national attention had on research of sickle cell during the '70s?

Beutler: You mean where do I think it is on that curve?

Williams: Yes.

Williams: All right.

Beutler: I would say first of all, I ought to say that I've never been very much involved with it. I was on the Blood Advisory Committee of the Heart, Lung and Blood Institute, so I'm not totally away from it, but I've never had a sickle cell center. I think I've been on the outside advisory group of probably one in Los Angeles. So I think the perspective I have is a distant perspective, not a close perspective.

Williams: I see. Okay.

Beutler: My impression is that the best thing, and maybe the only really good thing that has come out of that whole program, is a probably better appreciation of the natural history of the disease. I think that is something that was not well known but could not be easily determined by any individual, and I think there is a better idea now of what the natural history of the disease is. There have been some other things, too, that are clearly worthwhile, but I'm not sure that this organizational structure would be required to make it happen. For example, stem cell transplantation in sickle cell disease. I'm sure that's been enhanced by having large collections of patients so that one could find the ones that are most likely to benefit. And I think we're very likely, the same business of concentrating patients may have been useful in clinical trials of things like hydroxyurea because there was a larger number of patients, so I think that in a number of areas, these centers have probably accomplished some good, probably not in proportion to the spending.

Williams: Yeah. It's interesting because, in thinking about the '50s and '60s, and certainly in conversations with other people, there is a depiction of the '50s and '60s as having a sort of disjointed effort, like some good things were done, but there wasn't a lot of coherent structure to what the studies were doing, and so you had pockets of study here, pockets there, and the

contribution that the '70s brought was the structure which sort of focused it, again, away from some of the basic science and more toward treatment. I mean, there is maybe a sense that during the '50s and '60s, a lot of the basic research focused on protein structure and function, understanding basic fundamentals about hemoglobin, but the whole idea about treating patients with a very painful disease, so now the focus had gotten lost. And so that's what the program brought.

Beutler: But as you see from our people in '59 or '60, the focus was there, and since there weren't any modalities.

Williams: Right.

Beutler: On the other hand, penicillin prophylaxis, for example, the kind of things that the pediatricians were able to do, I think that was probably enhanced by the program. I suspect it was a very inefficient way that if, instead of doing this probably politically very advantageous thing of forming centers and so forth, if there had been RFPs for programs on prophylaxis and programs on hydroxyurea could have been done. Even the natural history program could have been done.

Williams: Right, yeah. Like I said, I mean, I guess the jury's still out on this whole issue. There are certainly sides that presented a picture much like what you said, that the natural history is thought to be one of the greatest contributions, I mean, that you could actually follow the natural course of a disease and have some understanding of what you can expect, and that had not been done previously.

Beutler: Yes. And I might say it's interesting that there are many diseases where this has not been done, and some that I've worked with. In fact, two that I've worked with in more recent years, we've done natural history studies, and the result turned out to be very different from the perception of physicians of the disease. One is in Bechet's disease, and there the prevalent thought, which is pushed by the pharmaceutical industry, which

has a big profit motive, is that this is a progressive disease that gets worse and worse. It's turns out that's really not true, not in adults. It's only in the children. The adults with mild disease always have mild disease. No one had ever really shown that. Then, most recently, we've shown that hemochromatosis, that the genotype of homozygous hemochromatosis is quite common, as had been known, but that these patients don't have symptoms. The rate is only about 1 percent.

Williams: Really?

Beutler: And people had been saying it's 95.

Williams: Really?

Beutler: Yeah.

Beutler: It's very important because people have been going around screening for the disease, and they figure they're saving a lot of lives, and some of it is based on considerations like if these people have arthritis. Well, these are older people. They didn't have any controls. We had controls. So anyway, so those are just two diseases I've been involved in, but I think that you could probably look at a variety of other disorders and have a lot of misconceptions and, in the case of sickle disease, I think the sort of systematic investigation was helpful. And it forms, I think, sort of a baseline to measure therapeutic success.

Williams: Which is what was missing. And I think that feeds into this whole notion of the unorganized manner in which a lot of the research earlier had proceeded.

Beutler: Well, see, I think that you need a certain amount of organization in large clinical studies or natural history studies, but you don't really need organization in the basic studies. In fact, I think it's probably harmful.

Williams: But if you want to bring the basic studies to, you know, if you want to move it from the laboratory to the bedside, from the bench to the bedside, that kind of phrase, isn't that where the organizational structure . . . I

mean, if you don't have it, would you be concerned that it might stay in the bench?

Beutler: I wouldn't be. I think in a disease like that, with as many people as have been interested in it, I think if you have a treatment, they will come. That's kind of what I think. I mean, there are really only two treatments that have emerged that are practical. One is hydroxyurea and the other is transplantation. Now, I know transplantation would have gone forward without the sickle cell centers because it was done rather extensively in Belgium before it was ever done here, and it would have been done here by the marrow transplant centers. Didn't need sickle cells. And hydroxyurea, I think that with promising results, I'm sure that investigators like Sam Charache, who played a major role, would have been able to get NIH funding for a good study, single or multiple institutions. I don't think he would have had to have a sickle cell center. He would have had to have funding; he would have had to have funding. But could the money have been spent in a more efficient manner?

Williams: Right, right. Yeah. And I don't even know if Johns Hopkins has a center. I don't think so.

Beutler: Maybe not.

Williams: I think that's true. Well, that's -- like I said, that's sort of, at least what conversations about the '70s will sort of bring up, I mean, both sides of the coin. I mean, was it necessary? What did it bring to light? Would these things have occurred without them? Maybe, maybe not. Did it expedite things?

Beutler: Well, I think that one of the things that did happen, I'm sure, is that it brought more people into the field who really were not helpful.

Williams: Oh.

Beutler: I mean, in other words, that people who couldn't get funded for doing what they were doing said, "Well, I can get a job in the sickle center, so

I'll putz around there a little bit."

Williams: Right. And then you had a whole crop of them.

Beutler: Yeah.

Williams: And that's why the '70s has been harder for me to take apart, to disentangle. I mean, at least with the '50s and '60s, there's a series of name researchers, and they published multiple papers and there's a natural, logical structure that you can follow. And then we started to look at the '70s, you see a lot of sporadic papers, people who appeared and disappeared. It's a lot harder to track some of the research that.

Beutler: That's interesting, yeah. I wouldn't be surprised _____.

Williams: Yeah. I mean, conceptually, I'll have to look at the '70s in a very different way.

Beutler: You must be looking at the history of urea.

Williams: In terms of . . .

Beutler: In terms of how it started, how it ended.

Williams: Right.

Beutler: Why it -- I mean, it created quite a furor.

Williams: Yeah, with Murayama and Albano and that whole saga.

Beutler: Yeah.

Williams: I have been tracking it. I think the question I have is to what extent do I want to really follow that story?

Beutler: Well, I mean, one of the questions, which is quite relevant to what we're talking about now, is, did the sickle centers play a role in that? I don't know.

Williams: I don't think so. I mean, they came after. That was pretty much on its last legs.

Beutler: Is that right?

Williams: Yeah. By 1972, there were some clinical studies run that basically showed that the urea, really good controlled studies were run that showed that urea

had minimal if any effect.

Beutler: Which was obvious from the beginning.

Williams: Yeah, to inhibit polymerization were just unreal, and the diuretic effect of urea, I mean, there were just a whole body . . . So by '72, that had pretty much disappeared, but there was a lot of sodium, potassium cyanate studies that I think Cerami and Manning were beginning to cultivate, and carbamylation studies.

Beutler: That was, you know, scientifically, a really good idea. But it turned out to be that it was a disaster.

Williams: Right.

Beutler: And then something else that happened that I never really was able to follow was that there were studies of in vitro carbamylation. And do you know what ever happened to those?

Williams: No, other than the neuropathies .

Beutler: Well, the neuropathies were the big problem, so then people had the idea that if you take the blood out of the patient, carbamylate it, and wash away the cyanate and put it back in, I mean, that gets to your issue of selectivity. Nothing else, carbamylate except, so that that might be a good way to treat the disease. And there was a study, I think, in Kansas or one of those, but I don't know what ever happened to it.

Williams: Yeah. I probably have some beginnings of that. Like I said, you try to follow all of the different threads, it has been challenging. But I do remember that whole sense of taking the red cells out, carbamylating them, washing them off, and then putting them back in. But I thought that also had some sort of major neurotoxic effect even then. I don't know. I'd have to look and see.

Beutler: It shouldn't have, but I never really followed it. I don't know whether it didn't get done or didn't work.

Williams: Right, right. Yeah, I know. I'm aware of those studies. But, right. I am

following the urea, and like I said, the extent to which, what's the lesson learned from that. I guess I'm trying to capture when I talk about that, I mean, more than just to say it was a body of research essentially went nowhere perhaps.

Beutler: Are you familiar with the studies that were done by Samuel Briggs [spelled phonetically] on bicarbonate?

Williams: Yeah, very early on, just the changes of pH and following that whole thread.

Beutler: And, you know, they looked pretty good, but I think that later control studies showed little or no effect.

Williams: Right, they did.

Beutler: But I think this is relevant to the issue that you raised about no interest in clinical studies. Yeah, there were. There were clinical studies that were done, and there were others, too. I mean, you've obviously looked at the literature very carefully. So centers weren't really required to get people to look at clinical agents, and there weren't any good clinical agents to look at either.

Williams: Right. There were a lot of things that probably contributed to why you see certain things in the '50s and '60s and saw certain things in the '70s. It may or may not have anything to do with the centers. I mean, it could just be the natural progression of knowledge, almost like we talked about with Pauling, where there was so much evidence that it just happened, and it could be the same with the centers, but people could attribute a lot of what they saw to the centers and to the national program. But one could make the argument that, again, causality, correlation, what we're really looking at here. And that's what a good research study, if it can't answer, it can at least raise a very compelling question, and that would be great if I could do that. We'll see. Well, I guess we're going to close out because I don't want to run you past. It's already three. But I did want to ask you

something about sort of the drug companies and this orphan disease status that sickle cell has and what you think the effect of that is. I haven't really gotten there in terms of my reading in the '80s.

Beutler: Well, in my experience, orphan drug status has been helpful in carrying out certain kinds of studies that I've been involved in, but not in sickle cell disease. For multiple sclerosis and hairy-cell leukemia and so forth but I didn't even know that it had orphan drug status.

Williams: It does.

Beutler: Well.

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