INTERVIEWEE: Dr. Hilliard Seigler
INTERVIEWER: Dr. James Gifford
DATE: July 18, 1994
PLACE: Dr. Seigler's Office, Duke Hospital South, Durham, North Carolina

SEIGLER INTERVIEW NO. 1

DR. JAMES GIFFORD: Durham, North Carolina, July 18, 1994. This interview presents Dr. Hilliard F. Seigler, director of the Melanoma Immunology Laboratory, Department of Surgery, Duke University Medical Center. This interview takes place in Dr. Seigler's office on the third floor of Duke Hospital South. The subject of this interview is Dr. Seigler's career and research interests and, more specifically, the work of the Melanoma Immunology Laboratory. Your interviewer is Dr. James Gifford. Also present, Mr. Charles Rutt. Dr. Seigler, perhaps we could begin by having you tell us something about your own career, and specifically how you came to be a surgeon with the research interests that you have now, and how you came to Duke.

DR. HILLIARD SEIGLER: Well, basically, my initial interest was in the field of transplantation. And I came to Duke after completing my surgery residency on a postdoctoral fellowship to work with Dr. Bernard Amos in Immunology. And I spent two years as an NIH postdoctoral fellow studying the field of immunogenetics. And during my time with Dr. Amos, I worked with Dr. Richard Metzgar. Our basic line of investigation was to try to define the antigens on the surface of human tissue that were recognized by the human immune response, and in an effort to try to accomplish two things: one, could we determine these antigens and their genetic control? And, secondly, could we define the human immune response to these antigens in an effort to try to improve the results with human organ transplantation?

And through the next several years, that was the focus of my investigations. So we were able to define many of the major human tissue antigens that are present on the surface of our

tissue cells and to define the immune response to these antigens. And, initially, worked in some of the very large families in the southeastern part of the United States, to try to determine the genetics. And then actually went to some relatively closed societies. So we looked at the Amish, for example, where for many, many generations these families were well documented. Some of the very large families in small communities in North Carolina, some of the mountain communities that through the family Bibles, as many as five generations might be defined. And then applied this initially to the renal transplant program that I was co-director of.

And as time went on and much of this area got well defined, I began to develop an interest in seeing what the immune response might be to now not normal tissue antigens that would be important in organ transplantation, but what might the immune response be to malignant tissues? And so the next period of my professional life was to try to define the antigens that appear on the surface of cells when they transform from normal cells to malignant cells, and did tumor antigens appear with that transformation? And, indeed, could define that these tumor antigens did appear. And if they appeared, then we wanted to look at what was the immune response now to tumor-associated antigens? And as a clinical model here, we chose, for one reason or another, melanoma. So, just as we had chosen renal transplants to work in the transplantation field—it's just an arbitrary organ—we chose melanoma in the cancer field. And through the years, now, have spent time defining, indeed, there are antigens that appear when cells transform from normal to malignant, and that there is, indeed, an immune response to these antigens.

And more recently now, we've begun to look at, what are some ways that we can enhance that response? In other words, how might we make the human more responsive, more immune to tumor antigens, and see if we could bring about rejection of cancer, which is the

opposite side of the coin from when we were looking at the transplant situation where we want to have as much genetic similarity and compatibility to get the host to accept the organ transplant in an efficient way. So, in transplant, you're trying to dampen the immune response; in the cancer field, you're trying to enhance it. So that is sort of where we are, at the present time.

And now we're taking what is a new step, and that is to say, Alright, can we add antigens to cancer tissue with the molecular biological techniques that are available to us today, to try to make cancer tissue more immunogenic—and by that I mean, enhance the immune response to it. And so, basically, what we're doing right now is adding genes to cancer tissue to make them more reactive in terms of the human immune response. So this is sort of the basis of gene therapy: That if you can change the genetics of the tissue, you can make it stimulate the immune response in an enhanced fashion. So that is our present mode of direction.

GIFFORD: From what year does your laboratory date?

SEIGLER: I'd worked with Dr. Amos from 1965 to 1967. And then in 1967, spent three years on my own career development award, and that went to 1970. And so from '67 to '70, that three-year period, I was on my own, and have been on my own since that time. So my own personal laboratory runs from 1967 to 1994, which is twenty-seven years.

GIFFORD: Given that cancer is such a big subject, you probably interact with other laboratories in the Surgery Department in your work. Is that so? And if so, what are they?

SEIGLER: Yes. We, through the years, have done a lot of collaborative work, Dr. Danny Bolognesi, with Dr. Dirk Iglehart, Dr. Kim Lyerly, Dr. Jeff Marx, Dr. Fran Ward, who's a geneticist that I've worked with now for more than twenty-five years. So we continue to do collaborative-type research.

GIFFORD: Could you elaborate just a little bit more what the current lines of investigation are, what you see the cutting edge in the field to be right at this moment, and where you expect to be going over, the next couple of years?

SEIGLER: Well, our basic interest right now is focusing around the field of gene therapy. So we're looking at different genes that we might genetically manipulate into tissue, so that we can change the genome of tissue, and thus make it more stimulatory in terms of the human immune response. So that's our major focus at this time. Actually, in 1970, we started the first immunotherapy at Duke Medical Center. And since 1970 have immunized more than ten thousand patients, specifically and actively against melanoma itself, in an effort to try to see what type of immune response we can produce. And is that immune response predictive in terms of improving the patient's ability to remain well? And so the immunotherapy, as a therapeutic event, really was initiated with this melanoma effort at Duke

GIFFORD: Okay. Let me switch perspectives here for a few minutes. You've been here, and your career at Duke has paralleled that of Dr. Sabiston, in chronology, anyway.

SEIGLER: Yes.

GIFFORD: Can you say a little bit about how the department has developed over the time you've been here, what you see the major changes being?

SEIGLER: Yes, when I first came, the department was an outstanding department in terms of clinical efforts, providing excellent clinical care of patients. It sort of set the standard in this area for clinical care. But what I've seen happen with Dr. Sabiston's leadership is that it has reached a national and international reputation in terms of basic and clinical research and teaching. So through the years, the faculty has grown a great deal, to where now we have a number of

outstanding investigative faculty involved with a variety of both basic and clinical science research. So it's changed majorly in that direction.

GIFFORD: When you speak of clinical work, what exactly does that mean?

SEIGLER: Well, I think clinical means, relates to human beings, whereas basic can just address basic scientific hypotheses, and experiments to test those hypotheses. But once it involves humans, then you ought to say that it's clinical research.

GIFFORD: Alright. Why do you think the change came when it did?

SEIGLER: Well, I think a couple of things: Number one was, is that there was a recognition by Dr. Sabiston that if we were to assume and maintain our reputation and stay in the top four or five institutions in this country, we would have to progress as other institutions of our level were doing; namely, institutions like Harvard, Yale, Johns Hopkins, University of California. And certainly, that was the direction that they were going, and we saw the need to do the same, to maintain our position and our function in biomedical research and teaching, and keep at that level in terms of academic institutions.

GIFFORD: How would you characterize the research that went on prior to the time you and Dr. Sabiston arrived? Is there something that one can use in terminology to define the difference, to make a marker?

SEIGLER: Well, I think most of the research up to that time—and it was excellent research—but it was almost all clinical research. And since the late sixties it's been both clinical and basic. And, certainly, all of the residents that go through the training program since I've been here have had to spend two years doing research during their residency. Dr. Sabiston has always required the faculty to develop a research interest, to develop a laboratory, so that we would have the structure and framework here to be able to provide that environment for all of our medical

students and residents, and, indeed, many people that would come to Duke as postdoctoral fellows. So, trained in other institutions, but come here because we had the type of research atmosphere and functioning laboratories to provide that opportunity to people that wanted to work in a particular area.

And then, too, certainly, the progress that was being made in terms of molecular biology, genetic engineering, open-heart techniques, all of these came along during that period of time. And so we had the techniques and the tools to be able to do it. Whereas, they hadn't been available before. And sort of a parallel to that, for example, if we're talking about our focusing on gene therapy, it's only been in the last four or five years that you had the ability to clone genes, and then had the ability to be able to introduce these genes into cells, and make them become part of the genetic code of that cell. So, it's just general scientific development that permits you to do things that you would like to do.

GIFFORD: You mentioned the residency program. Could you talk about its structure and development during the time you've been here?

SEIGLER: Well, since I've been here, it's been a program that has stayed true to three major sites of energy: we have a junior program, and that's two years where we introduce the people into basic principles of the surgical sciences. And then they spend two years in just research, nothing else. And then they have to spend an additional four to five years completing the residency at the senior level. And we also develop, during this tenure, the idea of a surgical scholar. And so, if an individual completed the surgical residency, as they might in any institution, they could choose to spend an additional year, and during that year would focus in a particular area. It might be heart surgery, it might be organ transplantation, it might be surgical oncology. So this idea was to develop the faculty to be here, or other major institutions, in a

particular area. So they were true surgical scholars. These were not people that were probably going to go out into just private practice and learn the practice of surgery. But they were probably going to meet particular needs of this institution, or other similar institutions, in terms of faculty development.

GIFFORD: Did those students—how were they selected?

SEIGLER: They're selected by being the absolute top of their group. So there would only be—initially we only had one. Through the years we've had as many as four or five scholars, as we've developed the environment that can absorb that number of people. But they had to show outstanding abilities, and they had to pretty much reach the level that we could reliably predict that they were going to be major contributors here or elsewhere, in terms of the surgical sciences.

GIFFORD: So they're selected, basically, from the top of the group of senior residents?

SEIGLER: From the residents at their level. So, by the time they were into their chief residency year, which would be a minimum of their sixth year of residency, it might be even as many as seven years of residency, that if they were at the top of that group that was with them at their level, they might qualify to be a Surgical Scholar.

GIFFORD: Thank you, Doctor. Turning to the chairman of the department, can you describe for us Dr. Sabiston's leadership and leadership style?

SEIGLER: Well, I think Dr. Sabiston, through the years, has recognized the importance of having extremely strong faculty in all of the areas, and not just one. In other words, he didn't just try to build heart surgery, didn't just try to build transplant. But he saw the importance of having extremely strong subspecialties like orthopedics, urology, plastic surgery, otolaryngology. And so we had extremely strong subspecialties, which has been to the benefit of all of us. He also has maintained an environment of dedication, even though it's much longer than most programs.

There's an intensity of work here. There's a level of sophistication and accomplishment that is not present in most surgery training programs. And, for certain, there would be individuals that would come here, and interview, and just choose that that's not the life they wanted. And it was difficult to do, because you've got to remember, during all this time, a lot of other things were happening in our society of, you know, you can only work so many hours a week, or you need certain freedoms to express yourself, and that type of thing, that we really didn't address as being important parts of the makeup of our department. So, for many, many years we have maintained that level of intensity. And I think, in the long run, it's been one of the hallmarks of our success.

GIFFORD: Could you say—you've used that phrase twice: level of intensity. Can you talk a little bit more about that, what it is, how it expresses itself?

SEIGLER: Well, yes. I think that some programs might have requirements that an individual be on every fourth night, rather lax dress code, didn't require two weeks—I mean, I'm sorry, two years—of research. That an individual could go into a subspecialty after one year of internship. Those were characteristics that we just didn't want to adopt. We wanted to say that all individuals needed two years of basic education before going into a subspecialty. We maintained a strict dress code. We maintained two years of research being an absolute requirement. And felt that since people didn't get sick and get well every fourth night, that it required a little more intense input in attendance. That one might have to work as much as every other night, as opposed to every fourth night, because that's the way disease and people's convalescence occurred. Didn't occur every fourth night. And so these were standards that we remained true to.

GIFFORD: Did you find that there were any negative consequences to this intensity?

SEIGLER: Well, I suppose there's always some negatives to anything. But nothing of any magnitude of significance. Every year at the end of the year we always have a get-together when

the residents are finishing. And one of the constant themes through all this, one was how much pride individuals took in walking the walk and achieving their level of performance, and their very strong dedication and high regard for not just Dr. Sabiston, but the faculty as well. They felt that they had received the very strong support and benefit of both.

GIFFORD: Returning, now, to your own work, how has your work been funded over the years?

SEIGLER: It's been funded in three ways: one, the National Institutes of Health; secondly, the Veterans Administration on Merit Research funds; and private philanthropy, which would, of course, include industry.

GIFFORD: And has the balance among those contributors changed over the years?

SEIGLER: It's changed a little bit. I've been very fortunate, I feel, in that I've received more than $20 million in NIH funds, and that's a lot. We're very proud of that. I've had a continuous VA research grant for twenty-seven years; that's a very long tenure. And so we've, again, had a pride that we must have had a degree of success or productivity to have generated that type of constant support. And we have been approached through the years by industry as well as private givers, and have built up private research funds, as well. It's become increasingly difficult every year to get NIH support funds, because we're all realizing the shortcomings of federal dollars. And so it's much more difficult to get an NIH grant now than it was ten years ago. So our posture has been to work as hard as we could, be as productive as we could, and just hope that our priority score would permit us to maintain our laboratory.

GIFFORD: What changes have you seen in the students over the years?

SEIGLER: I don't think any. The students are great. They're outstanding. We get only the very best of students. Always have. And I've always felt that if you couldn't educate these students, you ought to change your life and do something else for a living. Our students are the absolute

cream of the crop. And they're not going to get into Duke unless they are in the upper five or so percent of their class. They're all exceedingly bright. And so it's not terribly difficult to take that type of student and be successful with them. I don't think we can take a great deal of credit for it.

GIFFORD: When you were talking about Dr. Sabiston, you talked about the fact that he was a bit unusual in that, instead of building up one area, he chose to try to strengthen the department in breadth.

SEIGLER: Yes.

GIFFORD: Where do you think his vision comes from, on that point?

SEIGLER: Well, I think that it probably goes back to his own experience. He was fortunate to be with a visionary, Dr. Blalock. He was at Johns Hopkins, which has always been in the top five medical schools in the country. Dr. Sabiston is an extremely hardworking individual himself, and, I think, has always been goal-oriented. And so I think it was just the natural direction for him to take. And his success probably stimulated continued efforts in this direction. He's always been successful in every endeavor that I've been aware that he's been involved with. And, of course, I've been with him now for almost thirty years. So I think that his formula must have been pretty clear to him, because he certainly has done very well.

GIFFORD: You mentioned a minute ago that NIH funds were getting hard to come by. It sparked in my mind the fact that Dr. Hart, in an earlier book about the first generation here, said that his success in building a Department of Surgery had come from the fact that there was an appropriate relationship between freedom and resources. And since resources were always in short supply, that meant that there had been a great grant of freedom which he had used wisely. Dr. Sabiston, if I understand the burden of the interviews that I've had correctly, has not had quite the same degree of freedom, because he has had to meet the expectations and standards of

so many outside agencies that contribute to the department, whereas Dr. Hart had very little of that. But people keep telling me that Dr. Sabiston managed to create for them the same kind of freedom that Dr. Hart had. People basically didn't worry about resources, and they were encouraged to follow their own lights, and so forth.

I'm not sure what the immediate future's going to bring. But it looks to me like we may be entering a situation in which both freedom and resources are curtailed, to some significant degree. The medical enterprise is going to be increasingly managed, and free-floating individuals will be less apparent, and the resource base is going to shrink. Does that accord with your vision of the future? And if so, how does Duke work to keep what it has built?

SEIGLER: Well, I think there is a degree of that present in our society. And it confuses me from the standpoint that we appear to be bound and determined to repeat some of the problems of history. We're going headlong into directions that other countries have tried, and have shown to be not successful. And I think our greatest hope is going to be the American people. I think the American people and their expectations of us are going to curtail or contain some of the political restraints that we're seeing come into our society in general, and medicine in particular. I'm just not certain that the American public is going to be shortsighted or sold as much as our government leaders.

GIFFORD: Doctor, I usually end these interviews by asking what question I should have asked that I did not ask, that would have illuminated our topic more generally or more completely. Is there a question in your mind that you thought perhaps should be asked, that needs to be answered?

SEIGLER: No, I don't think so. I think it's been very clear.

GIFFORD: Okay. Thank you very much, sir, for your time.

SEIGLER: Yes, sir.

end of interview