

BERT VOGELSTEIN, M.D. '74

22 December 1999

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Mame Warren,
interviewer

Warren: This is Mame Warren. Today is December 22, 1999. I'm in Baltimore, Maryland, with Bert Vogelstein. I've got to start with a silly question. You're the first person I've talked to who was actually born at Johns Hopkins.

Vogelstein: Correct.

Warren: Did you know you were destined to spend your life here?

Vogelstein: Oh, absolutely. My mother signed the standard contract. She agreed to deliver birth here and they agreed to train me and put me on the faculty when I reached the appropriate age.

Warren: Well, it's come to pass. So you grew up in Baltimore? Am I making the correct assumption?

Vogelstein: Yes, grew up in Baltimore, been here all my life, except when I went to college.

Warren: I guess you always knew about Johns Hopkins.

Vogelstein: Always knew about Johns Hopkins.

Warren: Did you always know you wanted to be a doctor? How did all this come to pass?

Vogelstein: Yes. Kind of when I was a teenager, I read a book put out by Hopkins, called *The Making of a Physician*, which impressed me and I thought I wanted to go to medical school, which I eventually did.

Warren: And did you want to come here? Did you know you wanted to come here?

Vogelstein: No, it impressed me that I wanted to come to medical school here, yes.

Warren: So when did you—you came to medical school and you did your residency—

Vogelstein: I did my internship and residency here.

Warren: So—

Vogelstein: And then I went away for a postdoctoral fellowship for a couple of years at the National Institutes of Health, and then I came back in 1978, and I've been on the faculty ever since.

Warren: When you knew you wanted to be a doctor, did you know you wanted to do research? That's one thing—you're my first research doctor that I've talked to. So I want to understand. Help me to understand how you choose to go down that path and what your days are made up of.

Vogelstein: Well, they're two different questions, how I chose to go down that path and what my days are made up of. Completely different things.

It's hard for me to remember when I developed an interest in research. Certainly by the time I got to medical school I knew I wanted to do research. I didn't know if I exclusively wanted to do research or whether I wanted to do a mixture of clinical work and research or whether I just wanted to do clinical work, but I knew I wanted to try research, which I did and I liked it and I kept doing it.

Warren: But when I ask what your days are made up of, do you see patients?

Vogelstein: No, I do not see patients. I haven't seen a patient in terms of a physician-patient relationship. I've obviously dealt with patients a lot, but I haven't examined a patient, been a patient's physician since my last day of residency in 1976, so that was twenty-three years ago.

Warren: So what I'm trying to understand, though, is so you do deal with patients.

Vogelstein: Yes.

Warren: What's the relationships of the researcher to the patient?

Vogelstein: Well, in my kinds of research, it's usually indirect. We do research on diseases, so we're always thinking about patients and working with patient material, and sometimes I meet patients because the work we've done has helped some of them, but it's an indirect, informal capacity. We do basic research on disease. We do not see patients per se. Others in our group see patients. It's a two-way street. Patients donate materials to us to help us identify what's wrong with them and the mechanisms involved, and then eventually we hope to provide information to patients which will help them or their families.

Warren: Have there been, through your education and through your career here at Johns Hopkins, have there been particular mentors, people who've made a difference to you?

Vogelstein: Sure, all through.

Warren: Can you tell me about some of them, please?

Vogelstein: Sure. My first mentor, my first experience in laboratory was Howard Dintzis. He was then the chairman of the Department of Biophysics. He, in a sense, taught me how to do research and has been a role model for me ever since.

Others who made an impact was Bill Zinkham. He was the chairman of pediatric hematology.

Warren: Tell me what you mean, that Howard Dintzis taught you how to do research.

Vogelstein: He taught me how to do experiments, how to formulate questions. He even taught me how to pipette. [Laughter] You know, research is partly an art, partly a science. You have to learn the art. You have to be an apprentice. Someone has to teach you. He taught me. I mean, is

that the kind of answer you wanted?

Warren: Well, I'm trying to understand something that I've never done and that I don't understand, so I'm the lay person. I'm the reader of this book, and I'm trying to understand.

Vogelstein: Research is a complex enterprise, just as medical practice is complex. You go to medical school and you learn a lot about physiology and anatomy and biochemistry, but that doesn't mean that you know how to treat patients. In order to treat patients, you actually have to treat patients. You have to see patients, to examine them, have to learn how to interact with them. That's the art in medicine.

Science is the same way. You take courses, you learn somewhat different things than a physician does, maybe biophysics, more detailed biochemistry, molecular genetics, lots of things, but you don't really know how to do research until you try it. You learn that in the laboratory by working in a laboratory. You learn how to work the tools, you learn how to formulate questions, you learn how to answer questions. It's the same kind of thing.

Just as a physician has to do an internship and residency after they're trained and get their M.D. degree, they just don't go out and practice. Scientists also do internships and residencies. They're not called that; they're called postdoctoral fellowships. But it's the same thing. It's an apprenticeship. It lasts for the same period of time, three to five years. And this is after they get their scientific degree, a Ph.D. instead of an M.D. And then only after that are they thought qualified enough to actually practice science and be hired, say, by a university to do research and to teach.

Warren: And from what I understand, you do a lot of that. You have a lot of postdocs here in your lab?

Vogelstein: Yes. Since I've been here in 1978, we've trained about—we've had the pleasure of working with about eighty young people either at the pre-doctoral levels or they're getting their Ph. degrees, or at postdoctoral, during their apprenticeship periods. Now they populate a faculty of partly in Johns Hopkins, but all throughout the United States.

Warren: And what do you think the responsibility is of the mentor to the postdoc or the student?

Vogelstein: Responsibilities are, during the mentoring period, to make sure that the environment is conducive to education, that the trainee is getting the education and practice that they need to prepare them for the next step in their career, and then to guide them on the career path that hopefully they're well suited for. Obviously it's going to be their choice, but the mentor can nudge them along ways which seem most appropriate for the individual and help them get to where they want to be.

Warren: What's the one thing you want your students to learn while they're with you?

Vogelstein: I guess the main thing I want them to learn is that cancer is—we work on cancer—that cancer is a disease and the most important things that they can spend their time on are research activities that are likely to contribute to the management of patients with the disease. Always keep the patients in the back of their minds.

Warren: And would you say that that's the most important lesson you learned in your education here?

Vogelstein: I think that I did learn that, but it was a complex way in which I learned it. The laboratory I worked on during medical school was a very basic science-oriented laboratory. I think that lesson got instilled to me more during the time that I spent learning how to be a

physician, people like Bill Zinkham and Paul Lietman, who acted as my mentors during the time that I spent in the clinic, in medical school and postdoc, postdoctoral period.

Another person who has made, and continues to make, a large impact was a mentor after I came back here on the faculty, was Don Coffey. Don Coffey is the mentor's mentor at Johns Hopkins.

Warren: Tell me what you mean by that.

Vogelstein: Well, he spends a huge amount of his time with young people, just trying to make sure they're on the right track. His door is always open to virtually anyone at Hopkins, but certainly people that he's helped recruit or participated in their training. And he's full of wisdom and always good to talk to. A lot of people, including me, have taken him up on his generosity frequently over the years, especially at the beginning, but even now.

There are other people, too, who aren't on the faculty now or when they made an impact, but certainly are associated with Hopkins. One of them was Ben Baker. Ben Baker was in the Department of Medicine here for a long time, and after he retired he decided that he would like to establish a really world-class program in colo-rectal cancer research, in part for personal, in part for professional reasons. He instigated a program which I now kind of direct. That was way back in the early '80s. And he's been a great supporter of us ever since then.

Warren: How is he doing? He's somebody I was hoping to interview.

Vogelstein: You'll have to go see him. He's okay.

Warren: He's okay? I've heard mixed things about his health.

Vogelstein: He's okay, except he's got bad arthritis, so he's in pain. But I'm sure he'd like to talk to you.

Warren: Wonderful, because I know he was in the World War II unit. I know he has a lot of different things—

Vogelstein: He goes back a ways. He's in his nineties, late nineties now.

Warren: I'm glad to know he's doing well.

Vogelstein: He just wrote me a note just a couple of days ago.

Warren: Great. Great. I'm glad to hear that. What makes you stay at Hopkins? I'm sure you've had offers from other places.

Vogelstein: It's my home. [Laughter] You don't want to leave home unless you absolutely have to. I don't know, I've always regarded it as home. No better reason than that.

Warren: Have there been any opportunities through the years that have been missed, things that you really thought should have been pursued, that weren't?

Vogelstein: In my lab?

Warren: At Hopkins. You interpret that how you want to.

Vogelstein: Opportunities that were missed? I think there have been a few people, faculty members, that I would have preferred would have stayed at Hopkins because they were very good, but they were enticed by other offers. I mean, I don't know if that's missed, because I don't know that necessarily anything could have been done to retain them. But, you know, I certainly would have liked to have seen them stay.

Obviously Hopkins develops a great crop of young people which are, when they're ripe, picked by other institutions. It's kind of a shame, but that's the way the world works. As I said before, I consider this place home. I like the atmosphere. I think it's a unique place, wonderful students, very supportive administration, and they let you do your thing. They try not to interfere.

It's kind of the same thing we do with our students and postdocs. We provide guidance and we provide resources, but we let them blossom themselves. Hopkins does that same thing with the faculty.

Warren: Now, I understand you've had some pretty astonishing "Eurekas" in your lab.

Vogelstein: Okay.

Warren: I'd like you to verbally take me into the lab and help me to understand what it's like when you find one of the answers you're looking for.

Vogelstein: Can't do that, because it's not what people think it is. It's not "Eureka!" It's nothing like that. It's you're working on a problem. In order to make progress on the problem, it usually takes years of concentrated effort and continuing very hard work. People in our lab work eighty hours a week. They're here all the time. They have a goal, each of them, and sometimes they appear to make an important step towards that goal, but the emotion that is elicited by the experiment that it's successful is not "Eureka!" It's, "Hey, this is really interesting. I wonder what's wrong." Because you're conditioned by months and months and years and years of failure. Every time something looks good, it's virtually always followed by a realization that it's not as good as it looks and something is terribly wrong.

So what happens is, even in those things that turn out to be as successful as you could possibly have hoped, the initial emotion is fear, not "Eureka!" Fear that it's wrong. And then it usually takes quite a long time, weeks to months, to reproduce the experiment and to rule out all the potential artifacts that could have caused the false excitement. So experimental science, which is the kind we do, certainly has its moments when one is very excited, but it is so difficult that that moment is fleeting. [Laughter] And rapidly overtaken by back-to-reality and a lot of additional

experiments to verify it or refute it.

So it's not an instantaneous process. It's a long, drawn-out thing. It's still very satisfying, but that's not the real satisfaction that people get from science. It's not those "Eureka!" moments. People who really enjoy science enjoy it because of the day-to-day, the little things that go right, and the underlying idea that you're working on something that can one day be important, that's what really makes scientists tick, is the little things that work. The "Eurekas" or reaching the goals come all too infrequently, you know, to really make a scientist satisfied, and sometimes they never come during your whole life. So I can tell you about some moments that we were very excited and it turned out we were excited for good reasons, but it wasn't really "Eureka!"

Warren: Tell me about those moments.

Vogelstein: Well, one of them, maybe this is illustrative. Susie Baker, who's a graduate student, back in the mid '80s we were looking for evidence of a cancer gene which we expected to be on Chromosome 17, and her goal was to find that gene. Now, back then no cancer gene like this had ever been found, so it was almost kind of a humorous thesis project. We really didn't expect her to find the gene; we just expected her to make some progress toward mapping where the gene might lie on the chromosome. But during the course of those studies, she evaluated a gene which was called P-53, and still is, which we didn't believe at the time was likely to be the culprit that we were looking for. But her research led her to evaluate that gene based on mapping data she had.

So she designed a strategy to look to see if it were involved, and she was sequencing the gene in a cancer, a single cancer which we picked out. And it was a Friday afternoon in December in 1988, which is, I guess, eleven years back, because now is December '99. It was in the room

next to us and it was late Friday afternoon, about three o'clock, and she was looking through her sequence and she said, "Bert, look. There's a mutation here. It looks like there's a mutation here."

So I looked at it and the mutation was not a very impressive one. It was the kind that you wouldn't think would make any difference, but it was a mutation. We looked at it and we both knew that it would be exciting if it were true, but we were both skeptical that it was real.

So the next step was to make sure that the change really was a mutation that was not found in the patient's normal cells, which Susie did. It took her about three weeks to verify that. Now it would take about half a day, but with the technology back then, it took quite a bit longer. And then we looked at other cancers, and every single cancer she looked at, she found a similar mutation.

It took us about two months to realize that we had discovered a cancer gene that was likely involved in most cancers in the world, and that was going to start a revolution in cancer research, which it did. P-53 was named Molecule of the Year a few years later. It's now the most active area of research in cancer research, any kind of research. It's been that way ever since Susie discovered it. So that was about as close a "Eureka!" as we get, but it wasn't "Eureka!" It was, "Hmm. This must be an artifact." [Laughter] So maybe that's a good example.

Warren: That's a great example. Where is Susie Baker now?

Vogelstein: She's on the faculty at St. Jude's in Tennessee. She just had a baby a couple of months ago.

Warren: That's great. That's another great accomplishment.

Vogelstein: Yes, absolutely.

Warren: Thank you. That's the kind of story I'm looking for, from the beginning all the way

through. So you tell me that your people put in eighty hours a week, and I believe it. Do you have fun here, too?

Vogelstein: We have lots of fun. [Laughter] But part of it is because our work is fun. It's fun trying to discover stuff. It's fun trying to be where no one has been. It's fun using a lot of toys. But it's more meaningful than fun. People do it not only because they enjoy it, but because it's meaningful to them. They know they're working on something that is not just a game. It can really be of use to people. But there's a lot of things that go on that people consider fun. You have to talk to them. After you talk to me, walk around the lab and ask them if they have fun.

Warren: I'd love to.

Vogelstein: Then you'll find out. Ask them what they think is fun.

Warren: Okay. Last question. I know the world comes calling here. I know what I'm doing with you is not unusual.

Vogelstein: Yes, it is. I don't grant interviews that often. [Laughter] But the invitations are not uncommon.

Warren: So is that a hassle, all the media attention that you get for what you're doing? I guess my question, I would think it would be a huge interruption to what you're doing.

Vogelstein: It is.

Warren: How do you handle it?

Vogelstein: I only agree to do things which I consider important, and the public affairs office helps. The only reason to engage in things with media—well, there are a couple of reasons. One is to make people aware that there really have been advances made that would help them. But second, and more commonly, it's because it's good for Hopkins. People recognize Hopkins. They

recognize that good things are being done and that medical and scientific advances are made. The public affairs office is very good here, has an excellent reputation amongst the media. I know that from what the media has told me. If they think something is important because it's an important media—amongst the media, there are obviously some that are more important than others, then they will suggest to me that it might be worthwhile. But they put up a good barrier. Obviously there's a lot of interest in genetics. This is the kind of work we do as well as cancer. So we could spend all our time talking to the media if we wanted. Right now we spend very little.

Warren: I'm going to throw one more question. You mentioned genetics. How about Victor McKusick? Has he been a part of your life?

Vogelstein: Well, Victor McKusick introduced me to genetics when I was in medical school, first year of medical school in 1970. He had a little book. Back then I think it was still in paperback, a little thing, a primer on genetics. And I loved it immediately. It was mathematical. As an undergrad, I was in mathematics. So it was the first thing I encountered in medical school that was mathematical in nature, and I immediately fell in love with the subject.

During medical school I went to Victor's clinic. Victor had a very famous clinic back then. I used to meet weekly and patients used to come in with all sorts of rare genetic diseases. It was just fascinating. I used to go as often as I could, and it's incredible, all those diseases now we understand, virtually all of them, right at the molecular level. Back then no one had any idea what caused any of them.

Warren: What was he like as a teacher?

Vogelstein: He was an unusual kind of teacher. I don't know how he did it. He didn't tell a lot of jokes. You know, some people tell a lot of jokes, they bring their subject to life that way. I don't

know exactly how he did it. Maybe it was just because of his very clear ideas of what genetics were and what was interesting, but you just got fascinated by the subject matter and the way he presented it. It was very straight, but it was spellbinding in a way. He's continued to do it. He teaches a course up in Bar Harbor. He's been doing that for, I don't know, fifty years, or seems that way. He's taught a whole generation of medical geneticists. He's the grandfather, great-grandfather now, I guess. So he's certainly my genetics mentor. He's the reason that I got interested in genetics. I didn't know it would be cancer genetics back then. He certainly didn't know. But that's what it turned out to be.

Warren: Well, he has a lot of children out there.

Vogelstein: Oh, yes.

Warren: I want to thank you so much. Is there anything you'd like to have included in this book that you want to say, that we haven't talked about?

Vogelstein: No, I think you've asked good questions.

Warren: Thank you.

[End of interview]