BARTON CHILDS INTERVIEW

December 12, 2001

1. The Early Years and Education at Williams College; Decision to Attend Johns Hopkins University School of Medicine

AM: It is December 12, 2001, and I'm with Dr. Barton Childs in his office at Johns Hopkins University Medical School. My name is Andrea Maestrejuan, and we're here to do his oral history interview for the Medical Genetics Project. We'll start off at the very beginning and I'll ask you when and where you were born.

BC: I was born in Chicago in 1916, February 29th, 1916. I am an adopted child, and that has amused me as a geneticist because I have no family history. But it's also been more than amusing in that I had nothing to worry about all these years.

AM: Why is that?

BC: Well, I had no family history of anything; therefore, I needn't be concerned if my father fell over dead at age forty-five or that my mother died at age fifty of breast cancer, or whatever. In fact, my mother did die at age fifty but of malignant hypertension. But that had nothing to do with me, and I had no concerns of the kind that geneticists are likely to arouse in people when they tell them they have a hereditary disease.

AM: Right. That's interesting. Did you have any brothers and sisters?

BC: I had three sisters.

AM: Older? Younger?

BC: Two of them were four years older, and one was a year and a half younger. They're all dead.

AM: Were the two older ones twins?

BC: Yes, they were.

AM: So you had an interesting kind of genetic family, so to speak.

BC: I did, because the two older ones were twins, and they were adopted too. I might remind whoever looks at this that the idea of adopting children in the teens of the twentieth century, it was a rare thing that anybody did. But we were all enormously fortunate to be adopted by who we were.

AM: At what point did you get interested in genetics or pursuing any kind of career, let alone a career in medicine?

BC: Well, I know one thing. I went to Williams College to undergraduate school, and I took biology, as anybody would who was planning to go on to medical school, and in the course of it, there was a section on genetics taught by a botanist. I didn't know, of

course, that all the originators of genetics were botanists **endnote 1**, so I had no sense that I ought to listen. He taught it in -- it was so boring that the one thing, I said to myself, that I'll never get involved in is genetics.

I only got interested in genetics -- I'm perfectly clear on how it happened. After finishing house staff experience here at Hopkins, I was invited to become Director of Outpatients in the Harriet Lane Home. My duty was to oversee the house staff, who were taking care of the patients, so I saw all the patients that came through, or nearly all. There were a tremendous number of children with anomalies, and I wondered what was known about them and read something about anomalies and learned that there were two ways to study them. One was to take something out of every bottle on the shelf and give it to a pregnant rat, and not surprisingly, the rat would have deformed offspring **endnote 2**.

That seemed a rather inelegant way of doing things, to me, so I found that the alternative way was to do genetics. The genes seemed circumscribed and rather fine in how they worked, and that seemed a far superior way to understand the production of anomalies. Since I had to have some kind of specialty of some sort, that being the way things were then and are now, I undertook to go to England to learn something about genetics.

AM: Before we move you to England, I want to go back a little bit and talk about what kind of expectations did you have growing up, from your family, in terms of the role of education and the role of career?

BC: I think that it was expected that I and my sisters would go on to college. I don't think there were any specific expectations beyond that. I was raised in a family where the intellect was important, so I rather expected that I would do something that would use my mind. That was the climate in which I was raised.

AM: At what point did you decide on medical school?

BC: I really have no idea. I can't tell you. I don't know.

AM: Do you come from a family of physicians?

BC: No. I have one uncle whom I always admired, and there may have been some subliminal influence from him. I followed his career. He's twelve years older than I, and I followed his career with the kind of interest that a boy would do with a grown uncle. But whether that -- I just don't really know. It was a subliminal decision.

AM: What were your options in terms of which medical school to go to?

BC: I applied to three. I applied to Harvard and to Columbia and to Hopkins. My suit at Harvard was declined. I was rejected at Harvard but accepted at Columbia and Hopkins. There may be something more than just subliminal about my uncle's career because he was a Hopkins graduate. While I thought at the moment I wanted to go to Harvard, I was happy to be accepted and to come to Hopkins. I hadn't been here more than three days before I was telling myself I was glad my request was refused at Harvard. (chuckles)

AM: And why was that? What was it about Hopkins?

BC: I think I didn't behave in college in the way that they expected at Harvard. I didn't do extracurricular activities with any zest or interest. I think, at the time -- let's admit that admissions techniques are imperfect, at best, and they're no better today than they were then; but I think they thought then to be a student at Harvard you had to take extracurricular activities seriously. That was my guess. I don't really know.

AM: I am struck in reading your book that you recently published, [Genetic Medicine: A Logic of Disease. Baltimore: Johns Hopkins University Press, 1999] you have quotes from Shakespeare and quotes from [Aristide] Briand, which is not typical in conversations with physicians and scientists that they can discuss Shakespeare all the time, or put it in their scientific work. I was just curious as to what kind of education did you get at Williams College, or what kind of education did you pursue? Was it broad in scope, or did you choose a specific scientific path?

BC: I was a chemistry major. But like, I suppose, many others -- I don't know. My mother was a highly educated person and read to us as children and certainly stimulated an interest in reading in me. So I think that's where my --

I hope that you noticed that those quotations in the book were very pointed and very directly related to the chapters that they headed. Many people just put in some sort of quotation and keep its relevance to the written material to themselves. But what I wanted in each case was something that would summarize in the most economical way what was in the chapter.

AM: And why choose to go outside of the medical sciences to find quotes like that?

BC: I think because they are so pithily -- the point is made so concretely and so economically. That was the point of the chapter, and I wanted people to come back to it after they'd read the chapter and say, "Oh, I see why Virginia Woolf is involved here."

AM: Okay. We'll be returning to your book, because I think there's a lot more to be said about -- it's a tremendous piece of work that you've done there, and your ability to move in different worlds, into the literary world and into the medical and scientific world.

BC: They really aren't separate. They really aren't separate at all. If only they were more conjunctive, we'd all be better off.

AM: Why do you think that’s the case that they aren't?

BC: I have no idea. I don't know. I have no idea.

AM: But you do think that we shouldn't have to talk about literary worlds and scientific worlds.

BC: I only think that -- and this is not an idea of mine. There are many people engaged in medicine who are struggling as best they can to show medical students and teachers of medicine this continuity between literature, or whatever you want to call it, that kind of thought and the kind of thought that goes on in medicine. They're one and the same.

AM: How did your training in medical school, in regards to genetics, differ from what you

received from the botanist in undergraduate school?

BC: There wasn't any.

AM: There wasn't any genetics whatsoever.

BC: None.

AM: Why did you gravitate towards pediatrics as opposed to some other kind of specialty?

BC: There was very little pediatrics in the curriculum, so I really had no opportunity to compare pediatrics with medicine. I knew I didn't want surgery. So I planned to do medicine. In those times, people often spent the summer as a substitute intern. It gave the real interns and assistant residents an opportunity to have a summer vacation and students could fill in the empty posts. So I decided to do a summer of pediatrics because I wasn't ever going to get any in medical school, and I wasn't ever going to see children again, so I wanted to sample. I enjoyed it enormously and did it reasonably well, I guess, because the resident at one point came and said that he had talked to Dr. [Edwards A.] Park, who was then the chairman of the department, about me, and he had suggested to Dr. Park that he offer me the job as an intern for the following year. I thought about it for maybe one nanosecond (chuckles) and agreed. It meant that I didn't have to go and interview with anybody or worry about whether I was going to get a job. And by then, I liked pediatrics a lot.

My whole life has been composed of drift in important ways. I don't know whether it's really drift or what it is, but it's drift at the conscious level. I mean, I made no conscious decisions there, and I told you, I don't really know how I got into medicine at all. It doesn't mean that my dedication to either medicine in general or pediatrics specifically was any less than it ought to be. It just meant that I don't -- I think that, in my life at any rate, a lot of major decisions have been made subliminally somehow.

AM: Okay. That's interesting. You also mentioned in one of the articles that you sent me about -- I think it was a speech you gave after you received an award -- that in addition to Dr. Edwards Park that Dr. Francis [F.] Schwentker and Victor [A.] Najjar at Johns Hopkins -- I don't have any dates to attribute to these --

BC: Well, Francis succeeded Park and failed in his mission as chairman because he committed suicide after he'd been in office for eight years, I guess. But he was a wonderful man and very helpful to me. When I first proposed to him that I go somewhere and study genetics, his response was, "Well, I've been thinking that you ought to do something of the sort, and that sounds all right to me." He then arranged with the Commonwealth Fund to get some money for me to go to England. That was done as I describe it.

2. Developing Interest in Biochemical Genetics; Training in England

AM: At this point that you're looking in the ward at pediatrics and noticing that there's a lot of anomalies in children, what was the connection between what you were observing and what you could learn about genetics to connect with these observations?

BC: Well, so many of the anomalies were familial.

AM: Again I don't have exact dates, but you went to Boston Children's Hospital [Children's Hospital Boston] for your residency?

BC: No. I was looking around for something to do after I was chief resident, and rather than go straight into practice, which is what I intended to do, I went to Boston Children's Hospital, where I was going to work with the guy who was doing some biochemical thing, I forget what. He moved after I'd been there maybe one or two months and went off to somewhere else, so I was left without any sort of direction. So I did a little bit of laboratory work in association with a friend who needed somebody to do some scut work, and I did it.

AM: What kind of scut work was that?

BC: Well, measuring amino acids in urine. The rest of the time, which was the vast majority of the time, I did my best to reap the bounties of Boston in every way I could. I read widely, not in medicine at all. It was one of the most rewarding years of my life. I made friends there who have been lifelong. I would recommend to anybody, after finishing house staff, to take a year and do something else. That's what I did. Again it was unpremeditated.

AM: Do you remember what you picked up and you read broadly? What subjects, what books, what lasting impressions?

BC: That's not relevant, please.

AM: Okay. At what point did you make the decision that going into practice, having a full-time medical practice, was something that you probably did not want to do, that you wanted to combine some aspect of research --

BC: This is another drift. I had returned to Baltimore a couple times to arrange with somebody to let me use their office in the afternoons, or whenever they weren't using them, and in return, I would take night calls. I'd sort of fix things up with the guy. Then I went to the spring meetings, the spring pediatric meetings, where Dr. Schwentker asked me if I would come and do the job I mentioned, become director of outpatients. Again my thinking took no time at all to agree. It didn't mean that I was suddenly dedicated to doing research or not to practice at all. It was another, Why not?

AM: Okay. And why England?

BC: Oh, that was easy. There were only two alternatives that I could see. One was Jim [James V.] Neel **endnote 3** at the University of Michigan **endnote 4**. He had just opened his place. It wasn't fully staffed. I was not unaware that it was in Ann Arbor, Michigan. I'm not fond of the cold. As opposed to London? I mean, where's the choice? Not only

London, but it was the one and only, I think, at the time, fully developed department of human genetics, run by Lionel [S.] Penrose **endnote 5**, who was known the world over as a preeminent person in human genetics and medicine. So I didn't see there was any choice. London was a wonderful place to be, and at the same time, all these people to teach me and from whom I could learn a lot.

AM: What year did you arrive in England?

BC: I went there in the summer of '52 and came home in the summer of '53.

AM: How common was this for an American who wanted to learn more about genetics to go to a foreign country to post-doc, I guess is what we call it now?

BC: I made that decision, and then having done so, I not unnaturally told my friends. I got so many raised eyebrows and dropped jaws that I disguised my purpose after awhile.

AM: In what way, and why?

BC: I said I was going to University College in London. I suppose people thought I was going to do pediatrics there. People would say, "What do you mean? That's fruit flies. Why do you want to study fruit flies?" I didn't try to convince anybody.

AM: And why was there this attitude -- and I guess I'm talking about what was the state of genetics at the time that people could not see the connections between studying some alternative model of genetics versus just human genetics?

BC: I don't know the answer to that. It wasn't that genetics was totally unknown to people in medicine. It simply wasn't a very exciting field. There was nothing really happening in it. It was dominated by the *Drosophilas* **endnote 6**, as indeed it ought to have been at the time. That was the state of its development and it was limited in medicine to the family history, or to gathering families, so we had the families. There was nothing to do about them.

AM: What genetic tools did you bring over with you to England, and then what did you --

BC: I didn't bring any tools.

AM: Methodologies.

BC: Nothing.

AM: And what did you bring back? What did your year in England do for you as a geneticist?

BC: Well, what I did there was to try to exploit everybody as much as I could. I fell in with Harry Harris **endnote 7** and spent more of my time with him than anybody. And when I came back, I was oriented to biochemical genetics and remained friends with Harris until he died.

AM: What did you see as the differences between, say, the state of genetics in the

United States and the state of genetics in England?

BC: Well, Harris is a good example. He was looking at blood and urine for evidences of genetic differences. No one here was doing that, as I remember it, anyway, and I could be wrong. Someone may rise to contradict me, but I don't think there was anything more to do in genetics than simply to note the fact that the disorder was familial. I suppose in a sense that was perhaps worthwhile in that a mother might think twice about having another child if you told her that her risk was something-or-other. She might not. But that was about it.

AM: Why did you choose to return to the United States as opposed to maybe stay in England and stay in the lab?

BC: I had a job here. I suppose that Schwentker would have agreed to my staying another year, but if I had just stayed there -- I had a family. I had a wife and two kids.

AM: Okay. At what point did you get married?

BC: Nineteen fifty.

AM: To talk a little bit about the historical context of when you started to become interested in genetics, it was an interesting period of time in the late forties and early fifties in that the social eugenics movement in the United States had pretty much gone by the wayside, but certainly we had a greater understanding of misuse of genetics as a result of the Nazi period and World War II. How did this kind of negative -- this notoriety that concerned early genetics affect the decisions you were making?

BC: I didn't know about it. I mean, I knew the Nazis were inhumane, and so on, but -- I had spent some time in combat against them, after all, so I knew them personally. But I didn't know that eugenics influenced medicine much. When I began to read widely, I observed that, but mostly, I thought it was just not very practical stuff or even very interesting, so my reading was directed toward more interesting things.

But that period was immensely interesting in the history of medical genetics because it was in the forties that [George W.] Beadle and [Edward L.] Tatum made their observation of the relationship of the gene to a protein **endnote 8**. That really was the spark that lit the flame of medical genetics, in my view, because at that moment, biochemistry was at a point where biochemists became interested in inborn errors. [Archibald E.] Garrod **endnote 9** was rediscovered, so to speak. Penrose, the guy I went to study with, had a very clear understanding of what Garrod had done.

So the mentality required to investigate inborn errors took form then, and it's never stopped. I mean, the discovery of inborn errors got onto an exponential pathway at some point and has never slowed down, really. The way to proceed now is to discover the actual gene and its actual protein and know the sequences of both, and so on. But then, it was possible to infer an enzyme by the analysis that you could make. I think it's of interest because it was quite independent of the double helix and all of that development for a long time. It was known as biochemical genetics, and Harry Harris was the principle figure in it.

Of course, later, as the gene definition became increasingly that which showed

relationships that the one gene/one enzyme didn't, then biochemical genetics was married, essentially, to molecular biology. And molecular biology has a bigger horn and blows it much more loudly so that people who were very good at it and would like to have devoted their lives to biochemical genetics, which could have been just as profitable as anything else, went into the other molecular area as well.

AM: Many have said that genetics really came of age with the molecular revolution, so why do you think it is that biochemical genetics wasn't recognized at the time?

BC: I think there's no question that -- obviously, the molecular way is more penetrating, broader, more -- for medicine, it's the last step in diagnosis. The ultimate step in diagnosis is to discover the gene, or genes, whose products are making the metabolic apparatus of the cells incongruent with the environment in which they are asked to work. I'm not suggesting that one shouldn't have gone beyond biochemical genetics. There are people who are still pursuing that path and, I'm sure, enjoying life just as much as anybody else, and to enjoy life in your work is what it's all about.

AM: When did you pick up Garrod for the first time?

BC: When I went to England.

AM: Why was it for you, you were more -- because it seems to me that you could stick with family histories and go genetics through that route versus the biochemical analysis. Why did you choose the biochemical route?

BC: It's the only way to go. Just doing family histories, there was no place to go. You had a family history, a pedigree that you could lay out and say this person is affected and that one is not, but you couldn't say who among people who didn't show the overt phenotype, who among them had the gene? One of the things that people did with the biochemical tests was to find heterozygotes among members of families of people who had recessive diseases. That was a big thing at one point.

AM: Okay. The other aspect of the historical context of this, besides the eugenics idea, was -- how aware were you about opportunities that the U.S. government was making in terms of studies of genetic mutations as a result of this increased use, kind of the discovery of atomic weapons and atomic power, that the government was now interested in funding studies?

BC: I knew about that, I guess. I did know about it because I know that there were people -- Jim [James F.] Crow **endnote 10**, for example, was greatly concerned, and others were also. There were meetings and publications, and so on. I went to some of the meetings, but I had nothing to offer.

3. Moving into Academic Medicine; On Becoming a Medical Geneticist

AM: We're going to go on a little tangent here because you mentioned something. At what point were your studies interrupted to serve in the military?

BC: After I had graduated from medical school and had one year as an intern in pediatrics. So I went into the army in the summer of 1943 and I got out in the spring of '46.

AM: Was there ever a moment that you thought that -- were you drafted?

BC: No, I wasn't drafted. They gave us a Hobson's choice. We could either sign up and enlist, so to speak, in which case they would take us as a physician, as an officer, or we could take our chances and maybe never be called, or be called as a private soldier. None of us wanted to be called as a private soldier, and there was a degree of recognition that there was a war on and that it was a legitimate war, and one did what a proper citizen would do and signed up.

AM: Did you have thoughts in the back of your head thinking, I'm going to end up in a field hospital in Europe somewhere and that's the last that's ever going to be heard from me again?

BC: The only way in which it would be the last you would be heard from would be to be killed, and that was always a possibility because I was with engineers and was in the field. The war was just an interim period. It had nothing to do with my future life.

AM: When you returned from England, you had a job.

BC: Yes.

AM: In terms of what choices you were going to be making about that job and the kind of work that you were going to be doing, how did you decide to -- starting a research program, or not?

BC: Well, I was urged to do so by the chairman of the department. That was the purpose of going to London, to learn how to do research, so what I did when I came back was -- the one thing where I differed maybe -- I certainly differed from Victor [A.] McKusick here, and I differed from other people -- was that it was my view that to set up a genetics clinic was the wrong way to go. I thought that I would be a resource for the department for people who had families with genetic diseases.

In fact, in the Department of Pediatrics at the time was Dr. Lawson Wilkins **endnote 11**, who was the principle figure in endocrinology in children at the time, and I noticed that he had lots of different kinds of families with familial properties. So if I started a genetics clinic, it would just be the kind of stuff that nobody else wanted, and I wanted to participate in disorders of real interest to me. So I declined to set up a genetics clinic.

I was helpful to people in the department in guiding them, and I wrote papers on their families, and it worked out just fine for me, as I saw it. But it was quite different from what most everybody else did. And I don't say my way was better. Perhaps it wasn't. I don’t know. It worked out all right for me.

AM: In terms of medical genetics as kind of an institution, how do you think that impacted what was going on in Johns Hopkins?

BC: Of course, in the early fifties, there wasn't any medical genetics. There was just a few people: [F.] Clarke Fraser in Canada [McGill University] and Victor [McKusick] and Arno Motulsky in Seattle [University of Washington] **endnote 12**. There were very few people who were constantly invited to go here, there, and the other place to give talks of what was this genetics stuff all about. Somehow the word got around that genetics was important, so I think we were all asked repeatedly to go to this place and that and give lectures on genetics. There was the American Society of Human Genetics, which had started in 1947, if I recall correctly, which didn't appeal much to me at the time because it was dominated by non-physicians. I perceived them as interested in human genetics, which was okay with me. I perceived myself as being interested in how genetics impinged on medicine. So I wasn't that attracted to the society for a while. Maybe others were.

AM: Did you feel that, because the American Society of Human Genetics was predominated by Ph.D.'s primarily -- and we talk now really about --

BC: They were doing quite different things. They weren't doing biochemical genetics much.

AM: Did you feel like having an M.D. put you at a particular disadvantage?

BC: No, I didn't feel at a disadvantage of any kind.

AM: When did you start thinking about making medical genetics more of a formalized endeavor for physicians?

BC: I never had that intent. I did what I was asked to do. I went around to this place and that. And then at some point -- I don't remember exactly when -- I did have a training grant. I got a training grant from NIH [National Institutes of Health] and people came to have teaching in medical genetics, as they did in Victor's place in the Department of Medicine [at Johns Hopkins University School of Medicine].

AM: You seem to me to have been fairly self-motivated to learn genetics and to go off to England and learn in a premier genetics lab, but how did you attract and motivate new medical students to learn and practice?

BC: There was very little -- well, at some point, I don't remember just when it was -- it was very early in the fifties, I think -- the medical school decided to have a course in genetics for the medical students. They employed Dr. William [J.] Young, who was a Drosophila geneticist, to teach it. He was in the Department of Anatomy, and he would have to do the dissections in the human body the day before he taught the students how to do it, at least in the first year.

But he recognized that Drosophila genetics wasn't totally appropriate for human beings and that there had to be more medical input, so he asked people like me and Victor to help out and participate in the teaching, which we did. That went on for a number of years, and I guess something in the way of genetics teaching has been going

on here ever since.

AM: In your own work, before you went to England, you were making some observations about the patients you saw in the pediatrics ward. Then you went off to England and learned some biochemical techniques to help you understand in a greater way, genetics, or how to understand some of these observations, or analyze some of these observations. How did you bring those two things back together in terms of developing a research program?

BC: I lost interest in anomalies altogether. And I did some things, I forget what, in the way of research after coming back. Before long, I became aware that I'D better give up doing laboratory research because I'm a complete klutz in the laboratory. I break everything in sight, and I spill things on myself and on other people. So I more or less stopped. When I had the training grant and had fellows, I could supervise them, and I think I did that adequately. They remained friends, at any rate. (chuckles)

But the time came when -- I forget what happened, but my training grant, I guess I gave it up somehow. No, I think it kind of melded into the training grant in the Department of Medicine. I think it was suggested, perhaps by the NIH, that we have one training grant, so mine disappeared. At that point, I did change what I did and got out of the laboratory.

AM: Before we make this shift to what you were doing out of the laboratory, how do you see your work on the inactivation of one of the X chromosomes in terms of the canon of what was going on in genetics at the time? Where did you see your own research fitting in?

BC: I guess it fitted in. It's just another aspect. Human and medical genetics is an immensely broad field and any part of it is fair game for investigators to mess with. I had an interest for a time in sex differences. It seemed that there were various ways in which males and females managed diseases, infections, and things like that. That interested me. The glucose-6-phosphate dehydrogenase interested me, for whatever reason I don't remember, but it did, and I spent a lot of time with it in various ways. That proved to be a way to test the hypothesis that one X chromosome in females was inactivated in each cell, and using glucose-6-phosphate dehydrogenase, Dr. [Ronald G.] Davidson, who was working with me at the time, demonstrated that all cells that derived from any given single cell and the active X was the same one. That was, I think, a clear cut demonstration that the Lyon hypothesis was proved. Other people had, by different means, made similar conclusions.

AM: Would you say it's about this time, in the early sixties, that you decide that you're too clumsy in the lab, that your talents lie outside, or away from the bench?

BC: I guess so. Something like that.

AM: Okay. So where could you go? If you couldn't do bench work, where were you headed?

BC: Well, I cast about at some point, but I felt perfectly safe in doing it because I had been awarded by the NIH a research career award. That was quite different from a research career development award. What the NIH did was to plan to have a program in

which they would support youngish to middle-aged people for the rest of their careers, giving them the opportunity to be more deliberate about what they did, perhaps.

That program lasted only about three years, or maybe four, or maybe two, because what the universities did was to proffer their most prominent people, if they were in the right age range, using the money that they were paying that person for someone else. And the NIH caught on pretty quickly to how they were being manipulated and terminated the program for any further new people but kept on paying until the end the people to whom they'd given those things.

It gave me an opportunity to think about what I might want to do. And I came to the conclusion that what I would like to do was something in behavior genetics. I thought I would get into that because it was so utterly badly done, and I thought I might be able to bring to the field some sort of genetic sense by studying reading disability, dyslexia. So for several years -- I don't know how many -- I did that **endnote 13**.

It came to nothing because, though we did a lot of work and produced a lot of novel information about this problem, it was unappreciated generally by authorities in reading disability to whom the idea that a child could be genetically different from anybody else was anathema, unacceptable. So we had a heck of a time getting anything published. We could get things published in the pediatric literature or the genetics literature, but that wasn't where we wanted it to go. Eventually, although I'd had my one grant in the thirty years, it all came to an end because we couldn't get anybody to publish our stuff. It was good stuff, too. But other people must have suffered in the same way.

About that time, I became emeritus, I guess. Nineteen eighty-one. And since then, I've been thinking and writing things that some people read and others don't. (chuckles) I've had more fun in this past twenty years, I guess. I've done research with other people, I've done a lot of things. I've helped Pat [Patrick C.] Walsh here in how to go about looking for genes in both prostate cancer and prosthetic hypertrophy. And I've helped a guy in medicine how to go about the genetics of inflammatory bowel disease, and things like that. And that's my career.

4. Career Commitment to Johns Hopkins University; Formalizing the Practice of Medical Genetics; Thinking Genetically

AM: I think I'll just go back and just ask a kind of factual type question, and then we can go on to this bigger area of some of your more current publications. I was reading through some letters between you and Joshua Lederberg **endnote 14**, and at some point in the late fifties, '58, '59, '60 --

BC: Where did you get those?

AM: They're actually on the Web.

BC: Oh, that's right. He turned over all his correspondence.

AM: That you at one point thought that you might leave Johns Hopkins, that you looked at [University of] Wisconsin and also Stanford [University]. What was it about that point in time that you felt like there were other areas or other institutions to explore, and then why did you ultimately stay here?

BC: Well, I think anybody who just is determined to stay in one place at the start of his career is a fool. I think one has to look at jobs. I had a lot of offers and opportunities to be chairman of a department of pediatrics. I looked at a number of them and decided I didn't want them. I didn't want to be a chairman of pediatrics. It was increasingly an administrative job. While it might continue to be, although I think it no longer is, a kind of job where you could help young people materially in a sort of hands-on way with their careers. I could see that was not going to last very long, if it hadn't already gone in the places that I looked at. So I didn't want to be a department head in pediatrics. I thought at the time that if I did, I'd lose my investment in genetics, which was primary to me. So that was out.

But Lederberg offered me a job at Wisconsin where I would be in part in pediatrics and in part in genetics. I went to see him, but he told me when I first got there that he'd already decided to go to Stanford, so I didn't pay much attention to the Wisconsin opportunity. Then the same thing came up at Stanford. I'm sure at some of his intervention. I did seriously consider that.

[interruption - tape off, then resumes]

AM: I think we were talking about your staying here at Hopkins, your choice.

BC: Oh, as opposed to going to Stanford. I don't know the reason. I probably was just comfortable here. I will say one thing about Hopkins, and that is that in all the times that I considered leaving or interviewed for a job, I knew that whatever I wanted to do that was different from what I was doing, there was somebody at Hopkins who would be an authority on it, not just somebody who was messing with it, but somebody who was an authority. That was always in my mind, that I didn't have to go to someplace else because somebody else was there whom I needed badly and nobody here. There was always somebody who could provide help in getting started on something. There were people here when I became interested in reading disability. There were people here who knew what there was to know, and I moved right into it with no difficulty. So it wasn't a place that I felt I had to leave. I was very comfortable. And my then wife started a

business of her own, and as that became more and more successful, it made it harder and harder to leave.

AM: What do you think the impact has been on your work that you have stayed at Johns Hopkins all your career?

BC: I haven't any idea. I don't know. I did what I wanted to do. Nobody was telling me what I had to do.

AM: Well, in kind of this path that you have taken, not necessarily by choice but by being presented with opportunities and taking them where they've led, you developed a trajectory in genetics from somebody who didn't really have any idea to a certain idea of what medical genetics means, at the same time that the field has also developed into a very formal sub-specialty of medicine. Johns Hopkins is one of the first to create a department of genetics in '57 or '58, I believe it is **endnote 15**.

BC: It wasn't a department.

AM: Institute.

BC: Not in 1957. I think maybe that's when Victor started his clinic.

AM: Moore Clinic, right, right.

BC: I mean, it didn't have -- maybe it had university standing. I don't know. I thought it was a part of the Department of Medicine.

AM: Right, it was. By 1979 the American Board of Medical Genetics is created, and by the early nineties, there's a medical college. So how do you compare your own development as a medical geneticist with the field in general becoming very formalized and institutionalized and a sub-specialty now that physicians can pursue training in?

BC: That's a hard question. I think one of my primary interests right from the beginning, really, was to how to help to bring genetic thinking into medicine, not genetics but genetic thinking into medicine. Early on, I would publish papers on research that I would do in medical journals rather than in the American Journal of Human Genetics. I gave talks on the need for better teaching in medical schools, and so on. I did a couple of surveys of what was going on in the United States. I don't know if I sent you any of that stuff. I wanted to see not just medical genetics taught in the medical school, but I wanted to see the medical enterprise of work to bring genetic thinking to other departments and to medicine in general.

I don't feel that I've been very successful in doing that, but that was one thing I was working on all those years, trying to see how it would be possible. And one way that I thought it might be possible would be to study genetics and disease as disease, not as diseases. I've tried to create a sort of formal set of principles that might express what was going on in medicine as principles of disease. Because you see, medicine is oriented entirely to treating people who have diseases. We've broken up into obstetrics and into neonatology and into pediatrics and into adolescent medicine and into internal medicine and into geriatrics or gerontology. And it's as if there was some way that all of these categories were separate. They're not. They're human beings who have a life,

however long it is. It's in perfect continuity with itself. What you are and what you will be tomorrow is a result of what you were yesterday, which was itself a product of what you were the day before that.

So if you're fifty years old and have a coronary occlusion, that may well have a lot to do with what you were when you were ten. Even in utero -- there is a movement among a few people, which may go someplace or may not, I don't know, who think that things get established in utero that determine -- they don't determine the disease later on but determine susceptibilities for later on in life. That seems reasonable to me.

But it's that kind of study of disease, rather than diseases, that I've been interested in of late. I don't know whether other people are finding it interesting, or not. I continue to get asked to go around and give talks, so maybe they are. I don't know.

AM: Just to flush this out a little bit more. When did your interest in genetics move from just doing things at the bench as some geneticists have done, spent their lifetimes cataloging the different genetic disorders, into -- it's clear by the seventies that you're starting to think along more of a philosophy of genetics than just a practical science of genetics.

BC: I guess if it's clear by then, that's when it started. I don't know. I don't mean to sound like a dumbbell or a fool, or something, but I've taken very few decisions of the kind that I'm going to give this up and I'm going to start this. I have tended to see my career as a continuity rather than a set of different enterprises. And I think most people do that. I mean, I think guys who are good in the lab stay in the lab, as indeed they ought. God bless them. The world needs them. But I was a menace to other people and to myself. (chuckles)

AM: Okay. Well, I would describe the eighteenth-, nineteenth-, and maybe even early twentieth-century science as a science driven by a lot of theories, and it wasn't until the twentieth century that we had the methodologies to actually add empirical evidence to these theories. What you seem to be doing in your work, at least since the seventies, is, with the molecular genetics, with the molecular revolution, there's so much empirical evidence and so little synthesizing, and it seems that's what you're trying to do, is provide a synthesis of this, particularly, I found your book that you published in 1999 on medical genetics quite an interesting -- it's not a textbook. It's, it seems to me, an attempt at creating a philosophy of medical genetics.

[interruption - tape off, then resumes]

BC: One of the things that this life has given me is the option to do anything I like at any time, because I don't have many appointments. Those are my appointments, and I probably only have two or three for this week.

AM: Okay. Well, we'll finish for today and start up again tomorrow.

December 13, 2001

5. Genetics as the Basis of Medicine

AM: It is December 13th, 2001, and I'm back with Dr. Barton Childs in his office at Johns Hopkins University Hospital. I thought we'd pick up today where we left off yesterday, and instead of giving you a long-winded question, which I was in the process of doing yesterday, just ask you about the work you've been doing since leaving the bench, so to speak, and, I guess, to describe what you meant. Yesterday you finished off by talking about principles of disease and not diseases. Maybe just explain a little bit more what you meant about this idea of principle of disease.

BC: It seems to me that everything that's happened in the past -- oh, either many years or few years, depending on -- everything that's happened is leading toward the recognition that genetics and genomics are the basic sciences for medicine. That is, if every protein is specified by a gene and if, as it seems to be the case, every pathogenesis is mediated by some protein or sets of proteins, then we have to conclude that genetics, or genomics, or both -- and I think it isn't really settled what the relationship between these two things is. Genomics is clearly the study of genomes, and genetics is the study of inheritable variation, so the two things go very well together. I think you have to conclude, if pathogenesis is always mediated by proteins, that every disease has some element of variability in it. And if you define disease as a consequence of failure to adapt, by which I mean a consequence of incongruence between some protein or set of proteins, some homeostatic device, then you have to accept that -- I'm getting mixed up here. You have to accept, one, that all diseases have some genetic element, and second, that genetics and genomics are the basic science for medicine.

That means that we need radically to change medical education. What I've been interested in, in the past ten or twenty years, is how to fit genetics into medical education in a way that does something new for medical education, which seems to me to have become oriented entirely around how to treat disease, how to diagnosis it and how to treat it. Which means that the students have to learn the facts, and the facts of disease seem to me to have taken precedence over the ideas, over the principles. I would have thought that a student is more likely to understand if taught in an intellectual milieu, if taught around a set of ideas. All medical students in all the clinical schools are very bright people, so they have no real trouble in learning what they're supposed to learn. Perhaps they forget a lot of it right after the exam, or at least, they say they do. I did that myself, I'm perfectly sure.

So it seems to me that what genetics and genomics does is to offer us a very sound context in which to teach medicine, but to teach it in such a way that understanding comes ahead of learning. That's what I'm after and what I've been writing about and hoping might happen.

AM: How successful have you been?

BC: Not at all. (chuckles) Not at all. The sociologists put it this way, as I understand it. They say that there are three kinds of people. One of them are people who are change agents. What they want to do is change something. Then there are people who are the opinion leaders, and they're the ones who provide the direction for the rest of the

population, who are followers. The change agents can spend ages saying what they say and trying to demonstrate even what they think, but until the opinion leaders get around to agreeing with the need for change and agreeing with the particular orientation of the change agents, nothing happens. But then, when something begins to happen, it happens very quickly.

I think what has happened recently very quickly is that people have accepted the gene as a very important -- perhaps the most important -- instrument of diagnosis. People have certainly accepted genomics. The next thing to accept is proteomics, which is the study of the description and function of proteins that are exposed by genomics.

When it's clear to everybody that you can't properly describe a disease except in the context of the genes that are involved in specifying the proteins that have mediated the pathogenesis, then I think the kind of approach to medical education that I struggle with will become the usual, but I think not before.

I don't know enough about how people learn to say why this kind of slow followed by rapid change occurs, but it's my view that we're in, right now, a real transformation in our grasp of medicine -- of disease rather, I think would be better to say. Up until sometime in the recent past, it seems to me, we operated on the general idea that the body is a machine and that it breaks from time to time and somebody has to come along and try to fix it. That, of course, is the doctor. But I think it's being recognized now that the body, while it has aspects of the machine, that machines are all made to a single pattern, and we've been operating on that assumption for a long, long time.

But I think that it is coming to be understood by us all that the body, while it has machine properties, isn't a machine in that everybody is different. You may say we've known that everybody is different forever because we can identify each other, but we have limited those differences, it seems to me, to the exterior, a person's behavior and looks, and so on, and haven't recognized that the variety observed in a person's face and body, and so on, derives from the variety within the cells. But I think that's coming.

6. Teaching to Think Genetically

BC: There's a second aspect to this transformation, I think, and that is that we're accepting increasingly that there is no linear relationship between proximate causes of disease and the outcomes. I think that what happened in the latter part of the nineteenth century when people began to recognize that there were many different kinds of infection, and the idea of infection was the most popular way to look at disease -- not that there weren't non-infectious diseases and not that people didn't recognize them -- but the model for thinking about disease, I think, was dominated by that of infection. So, people conceived that disease was a consequence of some unitary cause that led in some linear way to a unitary phenotype or disease picture, which in its turn, suggested some fairly straightforward means of treatment of that disease. In other words, there was a kind of linear relationship between causes and outcomes.

I think that one of the most important elements in this transformation is the gradual recognition that linear relationships don't obtain, that causes are multiple, whether of genes or experiences of the environment, so that what we're now calling complex diseases are clearly caused by not only the specific proteins specified by genes, themselves various, but also by a great variety in the kinds and numbers of experiences of the environment over the lifetime. So we have to take into account in relation to every disease three time factors. One is the genes, which have been inherited by the individual from the past; the second is the developmental trajectory that the individual has taken through life, developmental, maturational, and that of aging; and the third is the immediate experiences, which often can be perceived as precipitating the disorder.

So I think that this kind of thinking in terms of the individuality of disease, given the number of factors that go into it, we're likely to have to believe that everybody has his own disease, that the genes we inherit from our parents, it's a different set for each one of us. We're unique genetically, we're unique developmentally, and we're unique in the experiences we have all along the line. There's nothing linear there anymore, so we're faced with a complex set of causes that create pathology in a kind of dense sort of way involving many systems, more systems than we used to think.

And outcomes are, it seems to me at any rate, emergent phenomena, because I don't think, even if you knew all the genes that given person had, you couldn't predict on the basis of those genes and their proteins what the picture of a disease was going to be. It's hard enough if the disease is associated with a single gene to see a linear relationship between the gene and its protein and the outcome of the disorder.

In addition, we're recognizing also the continuity between the most simple disease and the most complex because there's no break. Monogenic diseases, we now realize, are not monogenic at all. We've always said that they had modifiers, but we didn't tumble to the fact that the single gene disease with its modifiers was not qualitatively different from the multigenic disease, some of those genes being more salient than others. So the difference between that and the monogenic thing has disappeared.

So, in these ways, we're getting insights into disease that we didn't have before. Further, we're observing that there's a kind of gradient or selected effect throughout life with regard to disease. We know that -- we're told, at any rate, I don't think we quite know it -- but we're told that at least the most accurate approximation of fecundity is about 25 percent. In other words, of 100 percent of conceptuses, only 25 percent arrive

to be born. That means there's an immense amount of disease in utero, and we're in the habit of calling that fetal wastage. That's a way of avoiding saying that it's disease, but it is disease. We know that a great deal of it is chromosomal aberrations, and we know that for every one example of a given chromosomal aberration that arrives at birth, many, many more die in utero.

Presumably, there are specific inborn errors of intrauterine life. But we don't know about them. Perhaps we never will. I don't know offhand quite how we'll know them, but given the concentration of inborn errors around birth and just after, one has to suppose that there are many of them, perhaps even more in utero, in this 75 percent of the losses of conceptuses. Then we know that around birth and for the first months and years of life, there's a heavy concentration of inborn errors but that by puberty, 90 percent of all the inborn errors that we know have declared themselves and that only 1 percent, or thereabouts, is to be observed after age forty. That seems to be telling us that the force of the genetic impact on disease is heaviest early in life and wanes. It doesn't say that there isn't genetic variability just as much, or more, in diseases of later life. It merely says that selection is most heavy against disease early in life.

Of course, this means that the kinds of diseases that one sees over the lifetime vary. I think this whole idea of change and disease processes throughout life is something that a medical student should dwell on and hear a lot about and think a lot about. Because if a student goes into internal medicine, let's say, he'll have patients that are fifteen and twenty and thirty and forty, and the idea of this fluidity of disease process throughout life ought to be uppermost in his mind. As it is now, it's not because we pay more attention to the organization of medicine than we do to the biology of medicine in that we divide medical responsibilities into obstetrics, neonatology, pediatrics, adolescent medicine, and so on up the line, and now increasingly including the problems of old age as another specialty.

The real folly of these divisions -- not as organizational devices, they're fine for that. But the real folly of this kind of organization with regard to the biology of disease lies in aging, I think, it seems to me. Because some of aging has to be a result of the kind of living that has been done in the past, as well as the kinds of genes that the specific individual has, so that, inasmuch as what we are today is based on what we were yesterday, and what we will be tomorrow is based on what we are today through a long, long series of days, there's evident there some continuity with regard to life which ought to be, again, uppermost in a doctor's mind as he sees people of different ages of life.

My efforts of late have been in trying to formulate the principles upon which our actions are based, with the idea that they might become basic to the teaching of medicine.

7. Medical Genetics as a Medical Specialty; Genetics of the Individual

AM: It seems to me you in your lifetime as a physician have seen the increasing compartmentalization of medical specialties.

BC: No question of that. When I came into medicine, all the big divisions were there, but there were no divisions within departments. There were specialists, of course, but they didn't see themselves as separate divisions. They didn't have the accoutrements of divisions, and that has hardened and made the department of far lesser importance, so that the leadership in teaching and in example-setting has fallen more and more to the division head and less and less to the department head. In my time, the department head was supreme, and as I look back on my experience then, I thought that was a good thing, because you got some sort of sense of what that aspect of medicine was all about. You got it in part through the department head, but the other people in the department all were generalists, with some exceptions. There were endocrinologists and there were certainly some cardiologists, and so on.

AM: In what ways has making medical genetics a sub-specialty helped and/or hindered, or neither, this rise of genetic thinking that you're discussing. And alternatively, how can we move away from this compartmentalization that is, it seems to me, preventing an encompassing genetic --

BC: Let me say, I don't advocate doing away with the compartmentalization. I think organization is terribly important, and we would be a mess without it. Specialization is important, and if I have something wrong with my heart, if I ever do, I'll want somebody who knows a lot about hearts and under a variety of circumstances. And we all do want that. I'm talking strictly about what goes on in the head as opposed to what goes on with the hands, as it were.

AM: How do you think medical education, or medicine in general, can change in order to increase this thinking about genetics?

BC: I think it's both simple and impossible. Simple because the basic principles upon which disease is founded, and medical factors has to follow those, should be simple enough. Leads of all kinds have come from the exposure of the human genome and that of other organisms as well. I think in the next five to ten years, we should have at hand the basic material for the formulation of a new kind of education for medical students.

What the impact will be of this kind of thinking and whatever other thinking is going on in which genomics and proteomics and genetics figure, I don't know. I'm tired of listening to people saying this, that, or the other thing is going to happen and the predictions of kinds of treatments, and so on. It seems to me that the predictions of kinds of treatments are cast in this linear mold. That's the way I see it. So I'm not surprised that we don't have gene therapy yet. I think there will be -- or I guess there are already one or two things that have been treated that way, and there are other things that are being done. But I think it's beset by problems because of the linearity of the thinking. I could be wrong, and I daresay that anybody who devotes his life to gene therapy would have a lot of arguments that would prove me wrong. But we're all entitled to opinions if they're based on any kind of thinking.

AM: You mentioned the paradigm or the main metaphor in medicine has been the body

as a machine, and the physician recognizes a breakdown in the machine and fixes this breakdown, and the patient has a role being a machine with agency to recognize that it's broken down and come to the physician. So with this new way of thinking, what would be the new metaphor for the relationship between the physician and the patient?

BC: I don't know. What I think would be new is that individuality would be supreme in thinking about the patient. The doctor would perceive each patient, would see each patient as highly individual, as unique. We all say that we're all unique and we recognize that we're all unique, but again, that uniqueness, I think, has been confined in the past to our appearance and the way we behave, and so on, and hasn't got down to the intracellular behavior.

So I think that the sort of main issue with the use of genomics and proteomics and genetics will be in the perception of the patient as a unique individual. A slogan might be, "Every person has his own disease." Well, he does and he doesn't. We name diseases for administrative purposes. We want to classify people with diseases into groups that can be manipulated and managed, or managed more or less the same. But I think that in the past, we've tended to perceive those people as all alike, not just the disease.

With the idea of common management, I think we've tended to see them as similar, and I think also we've tended to treat not the patient but the disease. Well, I'm guessing -- or hoping maybe is the better word -- that the recognition of individuality and uniqueness in each person may cause the physician to pay more attention not to the disease but to the patient who has the disease. Many patients complain that they're happy with the way the doctor dealt with their disease, but they would have wished that the doctor would pay some attention to them.

I don't just mean be kind or say good morning, or something. I mean that the doctor might learn enough about the patient to maybe even change the treatment a little bit to take into account the uniqueness of the individual. I don't mean at all that we don't do that in a way, but it's usually more empirical than it may be in the future when we know more about people's genetic composition.

Much is made of the possibilities of medicine for prevention with the knowledge of genomics and genetics. It seems to me that the logic of genetics is all in the direction of prevention and that the logic of genetics gives primacy to prevention. But our knowledge of genetics is so far away from that logic that we can't pay that much attention to it now and maybe for some time in the future. In some ways, we do. We have antenatal diagnosis and abortion, or otherwise. We have quite a number of genes that can be tested for diseases, genes that represent susceptibility to diseases.

But we really have a tremendous amount of work to do to try to understand the meaning of genetic risk factors, because we do know that three people with exactly the same gene may have three different outcomes and that people with so-called diseased genes may never get the disease, and so on. So I think there's an immense amount of understanding that needs to be brought to bear on how to deal with prevention using genetics. That's not to say that we shouldn't do it little by little by little, but with a lot of understanding. I fear that companies will get hold of every gene and produce a test and that there will be a lot of testing that will go no place and that will only benefit the seller of the test materials. I don't know what the future is for prevention. I would say in the long future, it's very good, but in the immediate future, I don't see how we're going to get on

top of the problems.

I'm more interested in, I think, for myself, more interested in changing the mentality. The mentality has to change before we're going to do any of these things and do them right. I think it will change, but I don't know when. I mean, the logic of it is really powerful. You're not going to have all thirty thousand genes, or whatever it is, known and their proteins known, and whatnot, and not use it. So there's powerful logic there. We just have to guide it.

AM: That's the subtitle of your book, *Genetic Medicine: Logic of Disease*. At least in the UCLA medical library, you find the book catalogued with other textbooks, primarily called medical genetics. How do you see your own work in comparison with the main textbooks that medical students use today in their curriculum?

BC: Let me put it this way. There are several of those textbooks that are absolutely first rate. If I were a student, I would want to study them. All I'm asking for is that we study them in an intellectual context, which has been lacking. That's all. At least, it seems to me to be lacking. I wrote that book with the idea of filling a need. It's not a textbook at all, it's a book of how to think about things, it seems to me.

AM: Do you use it in your classes? Well, you probably aren't teaching at...

BC: I don't teach much of anything anymore.

AM: Do you make sure that your colleagues who are teaching assign it?

BC: I don't know quite how to make sure of anything with other people. (chuckles) They do what they want to do. I know that some people around here, their minds have been affected by my thinking, so I'm not unhappy.

8. Advancing Public Understanding on Genetics and Genetic Thinking; Moving Away from Mendelism; Transforming Medical Education

AM: I may have misread this. We talked about your ideas mainly in terms of medical education and the medical community, but the philosophy that you kind of delineated in this book, you also mention society in general and also just how the general public is educated in genetics. How extensive do you see this philosophy, or this logic of disease, extending, and what does it mean for education for non-physicians?

BC: I don't see anything in it that's particularly difficult to grasp, as opposed to sitting down to read something of [Ludwig] Wittgenstein or something like that, which is beyond my grasp. I don't see these thoughts as particularly difficult, so I don't think they're beyond anybody.

As to public education, as you may know, the genome project [National Genome Human Research Institute] itself took a very advanced view of that and created this section called ELSI -- I can't tell you offhand what the E-L-S-I means **endnote 16**. But one element in it is education of the public in genetics, genomics, proteomics, and so on. The man who heads it is named Joe [Joseph D.] McInerny. He's a close friend and he and I meet frequently, almost once a week, and talk about his problems. So I'm an informal advisor to that group, and I think, may have had some influence. I think that McInerny believes that these thoughts are not difficult, only different, and that sooner or later, they can be brought to bear, that sooner or later, people will understand them.

Right now, I think that people, in a general way, when they think of genes, they think that genes are determining, that if you have a gene, you're going to get the disease. Or if you don't, at least it's going to have made you uncomfortable while you wait for the disease to appear.

BC: There's a big job for this educational outfit. The members are of all kinds. They include the AMA [American Medical Association] and the American Diabetes Association and radiologists, and you name it. So there is a potential for some sort of mass education that will have some of these thoughts in it, I believe.

AM: You mentioned that sociologists divide people up into three categories.

BC: That's what I've been told. I know nothing about sociology.

AM: Okay. Well, how do you view yourself? Are you an agent of change, a leader --

BC: I think I'm an agent of change, a change agent. I've certainly been singing a song that other people haven't heard.

AM: And why is that?

BC: I don't know. I think it's because -- I don't know. What we've done in medicine over the past hundred years has been highly satisfying in many ways. It's gone from very little to being able to do a great deal. I think the need for the change is that in the course of doing all these wonderful things for people, it's been done through treating diseases rather than treating the specificity of that particular person. That may be all right, but I don't think it is. I don't think it is, at any rate. I think it would be better if the specificity in

the person loomed above that of the disease.

AM: When you were first introduced to genetics, either in college from the botanist or from the lab in England, could you immediately sense that genetics could be this encompassing theory or philosophy? Was there an epiphany at some time in your career?

BC: No epiphanies. But I do think that I got a very advanced view of genetics at the Galton Laboratory in London because there I met people like JBS [John Burdon Sanderson] Haldane **endnote 17**, whose name may mean nothing to you, but it will mean something to many people. If anybody ever looks at this thing, many of those people will have heard of him. He was one of the greats in genetics, not necessarily human. But he took an interest in human genetics and even in disease and had many cogent things to say about how genetics and medicine would come to move together. Then the head of the place was Lionel [S.] Penrose, who had many advanced views. There was no question in Penrose's mind that genetics would become an integral part of medicine in time.

I think I got, from the start, an idea that up there a long way away genetics would play an important part. The prevailing views at the time were those of medical genetics, actually biochemical genetics and then medical genetics, because in 1956 or so the true chromosome number was discovered, and then immediately thereafter, chromosome abnormalities were discovered. And that set off a big to-do about finding chromosome anomalies in patients with, usually, developmental defects. That was how medical genetics developed separately from other aspects of genetics but then, little by little and increasingly rapidly, came together with molecular biology and molecular genetics.

But I never had any sudden view, and I think the kinds of thoughts that I have are possible only under conditions of genomics. I mean, when you don't know many genes and have no way of finding them, well, you don't have advanced ideas about them.

But one thing you see that genomics did that medical genetics couldn't do, and that is be relieved of the shackles of Mendelism. In medical genetics, to get at the ultimate goal, you had to take into account the distribution of the trait in families. With genomics, you don't need to do that. You can go right to the gene with a genome search, or something -- one of the various ways of getting at them. That has made, I think, a big difference and will make more of a difference and relieve medical geneticists of -- it's already done so -- relieved them of a constraint. And that constraint was imposed on the mentality as well, because you only think in ways that are possible for you. People are freed of that constraint, and it's an important one, it seems to me.

AM: We live in an age now, particularly after the molecular revolution, in which there's a whole bunch of new tools out there to discover genes now that the genome has been delineated. There's kind of an impetus to find out what all these genes do. So it seems to me that scientists, particularly the young scientists, are busy chasing their results and their gels for their next set of grants. So it's still a very empirically driven science. It's more things to do, results to create, than time to think.

BC: I agree with that.

AM: So how can one create an environment in which this genetic thinking at least has

time to take seed somewhere?

BC: I don't know. What you say, that people are preoccupied with the need to get results for the next application, are certainly right on. And that it takes up almost all of their time is equally -- and that medical education is in a doldrum right now has also been pointed out by many people, not least Kenneth Ludmerer, who has written a couple of books in the last ten or twelve years -- the last one came out in 1998 or '9 **endnote 18*** -- in which he points out that the people who have to pay attention to their grants have been long gone as teachers, which left people who are consultants in hospitals for patients but who, in the past, had time to do serious teaching. He points out that those people are now engaged in seeing more and more patients to make up the financial need of hospitals and that the students are just left to be dealt with in whatever offhand ways they can.

Let me say that I know people who are very ardent and dedicated teachers that are still around, so it isn't as if everybody's gone, but I think what he's talking about is the sort of general mood. I guess that's true. I don't know. I think that it's too bad and that those medical students deserve better and that medical schools are going to have to do something about it, but that's been said for years and they haven't done anything about it. I say they haven't done anything about it. I don't know that. I don't know of any recent survey that says this school does this and that school does that. But I'm taking that view because of Ludmerer's book and many other things written and published in Academic Medicine, which is the organ of the Association of American Medical Colleges, and that ought to be an accurate source of descriptions of conditions as they are. So it's not an ideal climate, I guess, to introduce changes in medical education.

The curious thing is that if you read Academic Medicine, you see again and again all kinds of suggestions for changes in medical education. Then you see the people who come along behind all these others and about every twenty years they point out that nothing has changed. I think what they mean is certainly not that the details of science haven't changed, because they have. I think they mean that the mentality hasn't changed and that, therefore, the science, as it's come into the system, has been adapted to the mentality. Ludmerer pointed that out in one of his books, and there have been any number of other people who have said that whatever you do to change the system, it doesn't change. And I believe that what they're talking about is the mentality doesn't change. But believe me, genomics and proteomics and genetics are going to change it. It would be nice to do it systematically, but it will be changed. I guess that's the way things go. Something happens and forces change.

AM: Are you on a one man crusade?

BC: No. I hope it isn't a crusade. At least my idea of crusades are full of violence. (chuckles) I don't think you can change people's minds violently. And I'm not alone. There are plenty of people who are looking for this kind of change and getting genetics introduced into medicine, and I think they've made a lot of progress. I just think that it needs to be systematized. I don't know. Maybe I just look for and hope for neatness in a system that hasn't any. (chuckles) Or doesn't see the need for it.

AM: I think my last question will be, Has your transformation from a young physician observing anomalies in the pediatric ward to a philosopher of genetic medicine been inevitable, or what role has serendipity played in creating the physician-scientist?

BC: (pauses) I have no idea. If I couldn't tell you why I went to medical school, I'm sure I can't tell you. I don't know. I guess it's -- if I were looking at somebody else and you asked me the question, I might have some more objective answers. I guess it's just the mentality that I have. I don't know. I look for answers. I find that hard to explain myself. I could probably do it if I were in a closet somewhere with nobody listening. I could probably come up with all sorts of explanations, but I think they might be quite embarrassing. (chuckles)

AM: Okay. Well, I think that is the extent of my questions, and I'll turn it over to you and ask you what have we not covered that you think is important?

BC: I don't know. I don't know. Don't forget, you're testing an almost eighty-six-year-old brain, so if I've forgotten something, I might be excused for it.

AM: Okay. I really appreciate you taking the time out of your schedule to do this interview.

BC: Well, I won't say that I've enjoyed it exactly, but it hasn't been as big a chore as I thought maybe it might be.

AM: Well, thank goodness. I'm glad to hear it. I've done my job then. Okay. Thank you very much.

BC: Sure.

END OF INTERVIEW

ENDNOTES

1. Most of the early pioneers of genetics were plant breeders. For example, Gregor Mendel (http://www.mendelweb.org/); Hugo de Vries (http://www.cartage.org.lb/en/themes/biographies/MainBiographies/D/DeVries/1.html); Carl Correns (http://links.jstor.org/sici?sici=0021-1753%28199512%2986%3A4%3C612%3AWDCCRG%3E2.0.CO%3B2-V); William Bateson (http://links.jstor.org/sici?sici=0035-9149%28195205%299%3A2%3C336%3AWBAMPO%3E2.0.CO%3B2-6); Wilhelm Johannsen (http://www.wjc.ku.dk/wilhelm/); Erich von Tschermak-Seyseneggand (http://www.eucarpia.org/secretariate/honorary/tschermak.html); and many others. For a brief history of early genetics, seehttp://links.jstor.org/sici?sici=0003-049X%2819650818%29109%3A4%3C199%3ATEM%3E2.0.CO%3B2-B.
2. For a similar experience, see F. Clarke Fraser's interview in this collection where he discusses the cortisone work of Hamilton "Happy" Baxter.
3. For a brief biography of James Neel, see http://www.ibis-birthdefects.org/start/neel3.htm.
4. The Michigan Heredity Clinic opened in 1941 and included geneticists Charles Cotterman, Lee Dice, and Harold Falls, a physician who became interested in the hereditary eye diseases. Neel joined the Clinic in 1946 and became the first chair of the Department of Human Genetics at Michigan in 1956. By the early 1950s, the Heredity Clinic was the most well-developed center for human genetics in the United States. It emphasized population genetics more so than clinical genetics, however. Other North American centers for human and medical genetics included Ohio State University, where Laurence Snyder was appointed Professor of Medical Genetics in 1932; Bowman Gray School of Medicine (now part of Wake Forest University) where William Allan was appointed chair of the first department of medical genetics in the United States in 1941, succeeded two years later by C. Nash Herndon; the Dight Institute at the University of Minnesota founded by Charles F. Dight and Clarence P. Oliver in 1941 and later directed by Sheldon Reed; the University of Toronto where Norma Ford Walker established the Department of Genetics at the Hospital for Sick Children in 1947; and McGill University and Montreal Children's Hospital where F. Clarke Fraser established a joint Division of Medical Genetics in 1950.
5. For more information on Lionel Penrose, see: http://links.jstor.org/sici?sici=0080-4606%28197312%2919%3C521%3ALSP1%3E2.0.CO%3B2-8.
6. For more information on the fruit fly, *Drosophila melanogaster*, as a model organism, seehttp://genome.wellcome.ac.uk/doc_wtd020807.html.
7. For more information on Harry Harris, see: http://www.archives.upenn.edu/faids/upt/upt50/harris_h.html
8. Beadle, George, and Edward Tatum. "Genetic control of biochemical reactions in *Neurospora*." *Proceedings of the National Academy of Sciences of the United States of America* 27 (1941): 494–506 (http://links.jstor.org/sici?sici=0027-8424%2819411115%2927%3A11%3C499%3AGCOBRI%3E2.0.CO%3B2-L). For brief biographies of Beadle and Tatum, see http://nobelprize.org/nobel_prizes/medicine/laureates/1958/beadle-bio.html andhttp://nobelprize.org/nobel_prizes/medicine/laureates/1958/tatum-bio.html, respectively.
9. For more information on Archibald Garrod, see http://www.dnaftb.org/dnaftb/concept_13/con13bio.html.
10. The interview with James Crow is available in this collection.

11. For more on Wilkins, see Fisher, D. A. "A short history of pediatric endocrinology in North America." Pediatr Res 55, no. 4 (2004): 716-26, available at: http://www.lwpes.org/aboutus/history.pdf.

12. Interviews with Victor McKusick, F. Clarke Fraser, and Arno Motulsky are available in this collection.

13. Childs published several papers on dyslexia, between 1972 and 1985:

a) Preston MS, Guthrie JT, Childs B. Visual evoked responses (VERs) in normal and disabled readers. *Psychophysiology*1974;11(4):452-7.

b) Finucci JM, Guthrie JT, Childs AL, Abbey H, Childs B. The genetics of specific reading disability. *Annals of Human Genetics* 1976; 40(1):1-23.

c) Preston MS, Guthrie JT, Kirsch I, Gertman D, Childs B. VERs in normal and disabled adult readers. *Psychophysiology*1977;14(1):8-14.

d) Childs B., Finucci, JM, Preston MS. A medical genetics approach to the study of reading disability. In Benton AL and Pearl D., eds. *Dyslexia: an appraisal of current knowledge*. New York : Oxford University Press, 1978.

e) Childs B, Finucci JM. The genetics of learning disabilities. *Ciba Foundation Symposium* 1979; (66):359-76.

f) Finucci JM, Isaacs SD, Whitehouse CC, Childs B. Empirical validation of reading and spelling quotients. *Developmental Medicine and Child Neurology* 1982; 24(6):733-44.

g) Finucci JM, Isaacs SD, Whitehouse CC, Childs B. Classification of spelling errors and their relationship to reading ability, sex, grade placement, and intelligence. *Brain and Language* 1983; 20(2):340-55.

h) Finucci JM, Childs B. Dyslexia: Family studies. In Ludlow CL, Cooper JA, eds. *Genetic aspects of speech and language disorders.* Academic Press, 1983.

i) Childs B., Finucci JM. Genetics, epidemiology, and specific reading disability. In M. Rutter (Ed.), *Developmental Psychiatry*. New York: Guilford, 1983: 507-519.

j) Finucci JM, Whitehouse CC, Isaacs SD, Childs B. Derivation and validation of a quantitative definition of specific reading disability for adults. *Developmental Medicine and Child Neurology* 1984; 26(2):143-53.

k) Finucci JM, Gottfredson L, Childs B. A follow-up study of dyslexic boys. *Annals of Dyslexia* 1985; 35: 117–136.

14. For this correspondence and more information on Joshua Lederberg (1925-2008), see http://profiles.nlm.nih.gov/BB/

15. McKusick was head of the newly created Division of Medical Genetics as well as director of the Moore Clinic for chronic disease.

16. For the Ethical, Legal and Social Implications (ELSI) Research Program, see http://www.genome.gov/10001618.

17. Johns Burdon Sanderson Haldane (1892–1964). For a brief biography of Haldane, see http://links.jstor.org/sici?sici=0080-4606%28196611%2912%3C218%3AJBSH1%3E2.0.CO%3B2-6.

18. Ludmerer, Kenneth M. *Time to Heal: American Medical Education from the Turn of the Century to the Era of Managed Care*. Oxford; New York: Oxford University Press, 1999.