

Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Program in Bioscience and Biotechnology Studies

BROOK BYERS:
BIOTECHNOLOGY VENTURE CAPITALIST, 1970-2006

Interviews Conducted by
Thomas D. Kiley
in 2002-2005

Since 1954 the Regional Oral History Office has been interviewing leading participants in or well-placed witnesses to major events in the development of northern California, the West, and the nation. Oral history is a method of collecting historical information through tape-recorded interviews between a narrator with firsthand knowledge of historically significant events and a well-informed interviewer, with the goal of preserving substantive additions to the historical record. The tape recording is transcribed, lightly edited for continuity and clarity, and reviewed by the interviewee. The corrected manuscript is indexed, bound with photographs and illustrative materials, and placed in The Bancroft Library at the University of California, Berkeley, and in other research collections for scholarly use. Because it is primary material, oral history is not intended to present the final, verified, or complete narrative of events. It is a spoken account, offered by the interviewee in response to questioning, and as such it is reflective, partisan, deeply involved, and irreplaceable.

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Brook Byers

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Biotechnology Series History—Sally Smith Hughes, Ph.D.*Genesis of the Program in Bioscience and Biotechnology Studies*

In 1996 The Bancroft Library launched the forerunner of the Program in Bioscience and Biotechnology Studies. The Bancroft has strong holdings in the history of the physical sciences--the papers of E.O. Lawrence, Luis Alvarez, Edwin McMillan, and other campus figures in physics and chemistry, as well as a number of related oral histories. Yet, although the university is located next to the greatest concentration of biotechnology companies in the world, the Bancroft had no coordinated program to document the industry or its origins in academic biology.

When Charles Faulhaber arrived in 1995 as the Library's new director, he agreed on the need to establish a Bancroft program to capture and preserve the collective memory and papers of university and corporate scientists who created the biotechnology industry. Documenting and preserving the history of a science and industry which influences virtually every field of the life sciences and generates constant public interest and controversy is vital for a proper understanding of science and business in the late twentieth and early twenty-first centuries.

The Bancroft Library is the ideal location to carry out this historical endeavor. It offers the combination of experienced oral history and archival personnel and technical resources to execute a coordinated oral history, archival, and Internet program. It has an established oral history series in the biological sciences, an archival division called the History of Science and Technology Program, and the expertise to develop comprehensive records management and to digitalize documents for presentation on the Web in the California Digital Library. It also has longstanding cooperative arrangements with UC San Francisco and Stanford University, the other research universities in the San Francisco Bay Area.

In April 1996, Daniel E. Koshland, Jr. provided seed money for a center at The Bancroft Library for historical research on the biological sciences and biotechnology. And then, in early 2001, the Program in Bioscience and Biotechnology Studies was given great impetus by Genentech's major pledge to support documentation of the biotechnology industry. Thanks to these generous gifts, the Bancroft is building an integrated collection of research materials--oral history transcripts, personal papers, and archival collections--related to the history of the biological sciences and biotechnology in university and industry settings. A board composed of distinguished figures in academia and industry advises on the direction of the oral history and archival components. The Program's initial concentration is on the San Francisco Bay Area and northern California. But its ultimate aim is to document the growth of molecular biology as an independent field of the life sciences, and the subsequent revolution which established biotechnology as a key contribution of American science and industry.

Oral History Process

The oral history methodology used in this program is that of the Regional Oral History Office, founded in 1954 and producer of over 2,000 oral histories. The method consists of research in primary and secondary sources; systematic recorded interviews; transcription, light editing by the interviewer, and review and approval by the interviewee; library deposition of bound volumes of transcripts with table of contents, introduction, interview history, and index; cataloging in UC Berkeley and national online library networks; and, in most cases, digital presentation at <http://bancroft.berkeley.edu/ROHO/projects/biosci>.

Sally Smith Hughes, Ph.D.
Historian of Science
Program in Bioscience and Biotechnology Studies
The Bancroft Library
University of California, Berkeley
November 2005

ORAL HISTORIES ON BIOTECHNOLOGY

**Program in Bioscience and Biotechnology Studies
Regional Oral History Office, The Bancroft Library
University of California, Berkeley**

Paul Berg, Ph.D., *A Stanford Professor's Career in Biochemistry, Science Politics, and the Biotechnology Industry*, 2000

Mary Betlach, Ph.D., *Early Cloning and Recombinant DNA Technology at Herbert W. Boyer's UCSF Laboratory*, 2002

Brook Beyers, *Biotechnology Venture Capitalist, 1970-2006*, 2006

Herbert W. Boyer, Ph.D., *Recombinant DNA Science at UCSF and Its Commercialization at Genentech*, 2001

Roberto Crea, Ph.D., *DNA Chemistry at the Dawn of Commercial Biotechnology*, 2004

Donald Glaser, Ph. D., *The Bubble Chamber; Bioengineering, Business Consulting, and Neurobiology*, 2006

David V. Goeddel, Ph.D., *Scientist at Genentech, CEO at Tularik*, 2003

Herbert L. Heyneker, Ph.D., *Molecular Geneticist at UCSF and Genentech, Entrepreneur in Biotechnology*, 2004

Keiichi Itakura, *DNA Synthesis at City of Hope for Genentech*, 2006

Irving S. Johnson, Ph.D., *Eli Lilly & the Rise of Biotechnology*, 2006

Thomas J. Kiley, *Genentech Legal Counsel and Vice President, 1976-1988, and Entrepreneur*, 2002

Dennis G. Kleid, Ph.D., *Scientist and Patent Agent at Genentech*, 2002

Arthur Kornberg, M.D., *Biochemistry at Stanford, Biotechnology at DNAX*, 1998

Laurence Lasky, Ph.D., *Vaccine and Adhesion Molecule Research at Genentech*, 2005

Fred A. Middleton, *First Chief Financial Officer at Genentech, 1978-1984*, 2002

Diane Pennica, Ph.D., *t-PA and Other Research Contributions at Genentech*, 2003

Thomas J. Perkins, *Kleiner Perkins, Venture Capital, and the Chairmanship of Genentech, 1976-1995*, 2002

G. Kirk Raab, *CEO at Genentech, 1990-1995*, 2003

George B. Rathmann, Ph.D., *Chairman, CEO, and President of Amgen, 1980–1988*, 2004

Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders (Hugh D'Andrade, David Holbeck, and Edward Penhoet), 2001

Niels Reimers, *Stanford's Office of Technology Licensing and the Cohen/Boyer Cloning Patents*, 1998

Arthur D. Riggs, *City of Hope's Contribution to Early Genentech Research*, 2006

William J. Rutter, Ph.D., *The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco, volume I*, 1998

Richard Scheller, Ph.D., *Conducting Research in Academia, Directing Research at Genentech*, 2002

Robert A. Swanson, *Co-founder; CEO, and Chairman of Genentech, 1976-1996*, 2001

Axel Ullrich, Ph. D., *Molecular Biologist at UCSF and Genentech*, 2006

Daniel G. Yansura, *Senior Scientist at Genentech*, 2002

William Young, *Director of Manufacturing at Genentech*, 2006

Oral histories in process:

Ronald Cape

Stanley N. Cohen

James Gower

William Green

Daniel E. Koshland, Jr.

Arthur Levinson

William J. Rutter, volume II

Mickey Urdea

Pablo Valenzuela

Keith R. Yamamoto

Interview History—Brook Byers

In these interviews, Brook Byers describes his upbringing, initiation into venture capital in the 1970s, becoming a partner at an inordinately young age at Kleiner Perkins, and participating in the foundation of two of the earliest biotechnology companies: Genentech and Hybritech. He tells of his subsequent decision to specialize in the new field of biotechnology and to spearhead capitalization of biotech startups in the 1980s and '90s. Byers has since been involved in the foundation and early direction of over forty high-technology companies, and is largely responsible for Kleiner Perkins Caufield & Byers' position in medicine, health care, and biotechnology investment. He brings this personal account up to date by describing his views on the biotech industry's relationship with the pharmaceutical industry, his many activities in community service and philanthropy, and his high-profile involvement in the 2004 campaign for the California Stem Cell Initiative.

Thomas D. Kiley, former general counsel at Genentech, conducted three interviews with Byers between 2002 and 2005. Byers reviewed, lightly edited, and approved the transcripts. By agreement with Genentech regarding the oral histories it supports, its legal department received transcripts of these interviews and all interviews in the Genentech series to review solely for current legal issues. As in all instances to date, no changes were requested. This oral history provides an important piece in the early history of Genentech and in the process also describes the rise and maturation of one of venture capital's most foresighted and respected practitioners.

The Regional Oral History Office, a division of the Bancroft Library, was established in 1954 to record the lives of individuals who have contributed significantly to the history of California and the West. We are pleased to include this oral history among the over 1800 ROHO has completed in print and electronic formats.

Sally Smith Hughes, Ph.D.
Historian of Science
Program in Bioscience and Biotechnology Studies
The Bancroft Library
University of California, Berkeley
June 2006

Interview 1: October, 4, 2002

[Begin Tape 1, Side A] ##¹

Kiley: Byers, session one, Tape 1, Side A. The interview is being conducted at the Menlo Park headquarters of Kleiner Perkins Caufield & Byers, on October 4, commencing at 8:55 in the morning. Good morning, Brook.

Brook Byers is entering his thirtieth year as a venture capitalist, and has, amongst other things been for many years the lead life sciences partner of Kleiner Perkins Caufield & Byers, a venture capital firm, universally regarded as premier amongst venture capital firms and one with a storied past insofar as the creation and evolution of the biotechnology industry is concerned. In your interview, Brook, I hope to get your perspective on the role you and your firm have played in the birth and evolution of biotechnology to the present point, as well as a perspective on where it's going from this point. That's a tall order, but why don't we begin at the beginning—and that is, at the beginning of your life. Will you tell us when and where you were born, please?

Byers: I was born August 2, 1945, in Belleville, Illinois, at Scott Air Force base, where my father was stationed in World War II.

Kiley: Was your father a career officer?

Byers: No, he was just in the Air Force during that time, during World War II.

Kiley: I had understood you were a Southern boy. When did you take up residence in the South, if at all?

Byers: Just right after the war, my father moved back to North Carolina. He had grown up in South Carolina and before the war had joined AT&T and worked for Southern Bell Telephone, and went back to that job in Raleigh, North Carolina. We then moved to various cities in the South. In those days, as typical of large corporations, a promotion involved a move. And so we moved every two or three years, much to the chagrin of the rest of the family of having to uproot all the time, to various towns in North Carolina and Georgia.

Kiley: In what capacity did your father work for AT&T?

Byers: He was what was called a district manager, which was a business manager of the local office.

1. ## This symbol indicates that a tape segment has begun or ended.

Kiley: Was your mother employed? Or was she a homemaker? Or both?

Byers: She always worked also. She was a real estate agent, and sometimes a secretary.

Kiley: How many siblings had you?

Byers: I had two brothers. We grew up very close, and have stayed close throughout our lives. We always shared a bedroom, and shared hobbies, such as ham radio, sports, and exploring the wilderness of Georgia, just outside of our back door.

Kiley: Your brothers are younger than you? Older than you?

Byers: One's older—two years older. That's Ken. Tom is seven years younger than me.

Kiley: What are they doing these days?

Byers: Ken is an entrepreneur, still in Atlanta. He went to Georgia Tech undergraduate and graduate school, and then got his MBA at Georgia State. He started his own business in the mid-seventies, and has gone on to start a few more companies, that all operated at the same time. Ken has been very successful—considered one of the leading technology executives in Atlanta.

Tom went to UC Berkeley undergraduate and graduate school, then worked in the software industry, where he became successful in building Symantec Corporation, and then decided at age forty to go back and teach at the university level. Today, Tom is a full professor at Stanford University in the School of Engineering.

Kiley: Are your parents living?

Byers: They both passed away. They lived in Atlanta. My mother passed away first from cancer, and that touches on some of the motivations I had to get involved in biotechnology. She died in the 1970s, and my father died a few years ago at age ninety-one.

Kiley: I understand you began your career in venture capital in 1972. I'm struck by the fact that your older brother Ken began his business in the mid-seventies, sometime after your venture capital career began, as did your younger brother Tom. Do you think you were influential at all in their career paths?

Byers: Oh, perhaps, in Tom's. I think Ken's was just a matter of timing in finishing graduate school. He had a family already, and he was getting work experience before leaving and starting his own company.

Kiley: Tell me about your early educational history.

Byers: Well, I went to high school in Atlanta. It was a public high school, academically an average one, but with great classmates and families. I was influenced by a teacher there, who taught science and math. Up until that point, I was very much an average student, and found my intellectual pursuits in building ham radio sets, talking to people around the world, and enjoying that. But this teacher turned me on, as we say of great educators, and encouraged me to go to Georgia Tech, which was nearby in Atlanta. Georgia Tech is a public university. It was very affordable at the time.

I went there, and was advised by college counselors because of my interest in ham radio to major in electrical engineering, which I did. I attended Georgia Tech on the coop program, which is a work study program, where the student, such as myself, goes to school fall and spring quarters, works winter and summer quarters and then goes straight through the senior year, so it's a five-year bachelor's degree, so I was able to earn all my expenses by working. I then, by that time, had had two years cumulative experience as an electrical engineer, and decided that that wasn't what I wanted to do. So, with the advice of the dean of students at Georgia Tech, with whom I had become very close, I applied to graduate schools of business. As fate would have it, I was admitted to the Stanford Business School, and came out in the fall of 1968 to attend its two-year MBA program.

Kiley: Did you apply to other universities as well?

Byers: For graduate school, yes, I applied to Harvard Business School, and Wharton, at University of Pennsylvania. And when I went to visit them, in the spring of my senior year at Georgia Tech, I had arranged interview trips with computer corporations and so on, in these various locations, so I could visit these graduate schools of business. It was in, I think, late March of '68. So, I flew to Philadelphia and visited Wharton, and went to classes. There was snow on the ground, and everyone was wearing suits. Then, I flew to Boston, and attended classes at Harvard Business School and there was snow on the ground, and everyone was wearing suits. Then, I flew to Palo Alto, California, via San Francisco Airport. It was spectacular weather, and the students were walking around in shorts and short sleeve shirts, so that made the decision easy. [laughs]

Kiley: I would like to observe for the reader that we're sitting in Brook Byers's office, looking out on a beautiful sunny California day, and that neither he nor I are wearing suits at this time.

Brook, are there colleagues who attended Stanford Business School with you, who are particularly memorable and come to mind? Were you networking in business school?

Byers: Yes, you know, I think the experience in college and universities, whether undergraduate or graduate, is of course, a mosaic of experiences. A lot of the

value comes from things done outside the classroom. And that includes people one meets. Classmates—I think what struck me at Stanford Business School was the variety of types of people, personalities, career interests, backgrounds. There were people like me who were very quantitative and had an engineering background. There were people with liberal arts undergraduate degrees, and work experience, and history, or public policy, or science, other than what I had been exposed to. That was very different for me, because Georgia Tech, at the time, was very much just an engineering-focused educational experience, and that was the prime experience of my life up to that point. So, there were people in the class that I think broadened my scope.

I think being at Stanford University had a huge impact on me also because it had a medical school. It was at Stanford that I first became intrigued with the idea of making a contribution to society. Attending Stanford University in the late sixties was an exciting and mind-expanding experience because there was a lot of turmoil going on in the campuses and anti-war protests. There was a lot of questioning by students about the historical organization of curriculum, about the role of the university in the world, about having, what was called at the time, a “world view”. This was all new to me. I think the experience, just that two years, at a university like Stanford at that time in history had a huge effect on me and set the groundwork for my being open to taking some of the decisions I did later about biotechnology.

Kiley: Before we go to that, let's step back to your undergraduate days and your studies in electrical engineering. What was it about those studies, or perhaps about the cooperative work program in which you engaged, that led you to conclude that electrical engineering, as a profession, was not for you?

Byers: Oh, I think that was just a personal decision, just a personal choice. I enjoyed the rigor of studying electrical engineering. It's a fascinating topic and the rigor of the math and the physics and describing natural functions and processes in formula and mathematics, and trying to understand them, and build systems. I liked all that part. I just couldn't find anything that I personally felt I wanted to do the rest of my life. So, I was still searching.

Kiley: Do you still maintain contacts today with any of the people with whom you attended Stanford Business School?

Byers: Oh, yes. I have friends who live in the local area too, and a couple of us had the good fortune of entering the venture capital business. It was at Stanford Business School that a pivotal event occurred for me, that led me to being in venture capital.

Kiley: What was that?

Byers: There was a series of what we called brown bag lunches that were held in the auditorium there. Once a week, outside speakers would come in who were business people or people from investment banking, or consulting, or other professions, and they would talk about their profession. It was a wonderful way to expose students to the realities of all the different things people could do when they graduated. One day, there was a panel of venture capitalists, and I really didn't know much about that profession. The three visitors were Pitch Johnson, Bill Draper, and Reid Dennis, and I was mesmerized by what they were talking about. What they were saying was that there is a revolution happening and going to explode in technology and science. Silicon Valley was growing, just south of the Stanford campus, in the Stanford Industrial Park, and Santa Clara, and Sunnyvale, and San Jose, what we now call Silicon Valley. At that time, it wasn't so obvious that that was an important industrial activity. Most of my classmates had planned careers and went off to New York to do investment banking and consulting. Working in real estate was the most popular thing at that time, as a way for people to succeed.

Kiley: And working in the snow and wearing a suit as well.

Byers: Well, yeah, that too. And so, I listened to what these three men had to say, and I remember sitting in that auditorium—I remember it today—I got goose bumps, and I just said, this is amazing; this just sounds wonderful that someone could have a job where what you're supposed to do is read scientific journals and engineering journals and the literature, and then meet entrepreneurs, and try to determine what is the next thing that's going to be developed in these products that's ten times improvement in performance or price, or some scientific revolution, and then how that can be transferred into products and markets, and how that will roll out, and how you can build fast-growth companies from scratch. This was all new to me, and to think that there was a job where people actually did that was amazing. So I think sitting there that day, I said to myself, I'm going to get a job doing that.

Kiley: You mean, I can do all this, and have all this fun, and actually get paid for it.

Byers: Yeah, right.

Kiley: Just for the record, what is Pitch Johnson's proper name?

Byers: Franklin Pitcher Johnson, Jr.

Kiley: He was then with Asset Management?

Byers: Yes, he had just formed Asset Management Company.

Kiley: I presume Reid Dennis was with Institutional Venture Partners?

Byers: He formed that later. He actually was with American Express Management in San Francisco, managing their public and private investments.

Kiley: And what was Bill Draper's association then?

Byers: He had just started Sutter Hill Ventures.

Kiley: What's your best recollection as to the year in which this brown bag lunch took place?

Byers: Oh, this was in the spring of 1970.

Kiley: Did any of these savants of venture capital in the spring of 1970, when they were talking about the technology and science revolution that was brewing, have anything to say about the life sciences?

Byers: I don't recall that they did. I don't think they did. No, all of venture capital at the time and start-ups and Silicon Valley and all of that was about semiconductors, computers, computer peripherals, maybe a little bit about communications, but that was all.

Kiley: When did you complete your Stanford MBA?

Byers: I graduated in June 1970.

Kiley: What was your first employment following your graduation?

Byers: I went to work for a consulting firm called Management Analysis Corporation. It was a consulting group comprised of faculty from Stanford Business School and Harvard Business School and some graduates. I was encouraged to join this by one of my professors.

Kiley: Did you consider seeking venture capital employment immediately on your graduation from Stanford?

Byers: I did. I attempted to get a job in venture capital and back then, there were only a few dozen firms around the United States, with not many people in it, so all told, the number of venture capitalists in the United States in 1970 was fifty, I would guess. So, the chances of getting a job in it was pretty slim and there was also a recession in 1970, so firms were holding back. I decided I would just make it a long-term goal and go out and get some experience.

So, I worked at MAC for about eight months. In my seeking to find what I really wanted to do in life, I left that, and joined a company called Advanced Memory Systems down in Santa Clara, which was a manufacturer of semiconductor memory and equipment.

Kiley: Brook, is it possible that before joining Advanced Memory Systems you were employed for a time at Behavioral Research Laboratories?

Byers: Yes, I was, for about six months, I worked at an educational publisher. What was interesting about that and Advanced Memory Systems was that both of them were small companies, just recently public companies, and I had a middle management position in both of them. But it gave me a real flavor for start-ups. Both of them had been backed by venture capitalists.

Kiley: Let's go back for a moment to Management Analysis Corporation. What was your job title there?

Byers: I was a junior consultant associate.

Kiley: What middle management position did you hold at Behavioral Research Laboratories?

Byers: I was a general manager in the publishing group.

Kiley: What sort of things did they publish?

Byers: Educational texts that went to K-12 schools, what was the rage then in program learning materials.

Kiley: What position did you accept at Advanced Memory Systems?

Byers: I worked for the CFO, and it was a little bit of a training program working in finance and marketing and manufacturing.

Kiley: Over what period of time were you employed by AMS?

Byers: During 1972.

Kiley: Would I be right in assuming that then you took another shot at the venture capital industry?

Byers: I did. Well, I had always been keeping my antennae up to try to hear of any opportunities in venture capital. The industry or profession, as we call it, was not much larger than it was, as I described in 1970, but was starting to expand because technology was taking off; Silicon Valley was growing. I heard in the fall of 1972 from a friend I had made who was working at Brian & Edwards, another venture capital firm in San Francisco, that Pitch Johnson might be looking for an apprentice, which was the way it was described to me.

Kiley: Who was your friend?

Byers: Dodd Fischer. So, I wrote a letter to Pitch Johnson and asked him to meet with me, and told him that I was very interested in the venture capital profession and would like to go to work for him as an apprentice, and described my background in engineering and with a business school education, and my interest in entrepreneurship. The only evidence I could offer of work experience was that I had worked for a couple of young companies. I had worked for three in a period of two years, which I'm sure was not very impressive to him, from a "staying with a company" point of view. But the point I tried to make to him when I met him was that I had a varied experience [laughs] and also that I had perhaps the intellectual curiosity that would go with the profession. Of course, that's all a stretch. I think what Pitch was interested in was the passion I had for wanting to do the work.

Kiley: You learned that he was interested in that passion because in response to your letter, he met with you?

Byers: He met with me, yeah, in November of '72. I was *thrilled* by how it went, and I think he had some applicants he was considering. The long and short of it was that he went ahead and hired me and I started in December of '72.

Kiley: How large was Asset Management as you found it?

Byers: It was just Pitch and myself. Now, Pitch had been in venture capital for about ten years. He had come out to California to join Bill Draper, and they formed Draper and Johnson and had been partners throughout the sixties. Then Pitch went on his own and formed Asset Management; Bill Draper formed Sutter Hill, all in the late sixties. Pitch was an independent practitioner of the craft in the early seventies, so I was his first employee, and came to work for the master, in a sense.

Kiley: I've often heard him described as one of the pioneers of the venture capital as currently practiced. Tell me a little bit about Pitch, his background, and his investment style.

Byers: Well, Pitch grew up in Palo Alto, went to Stanford undergraduate where he was a champion track star. Then, he went to Harvard Business School, and upon graduating, Pitch went to work in the steel industry. He had an interest in doing something very active and producing things in a tangible way and was drawn to the steel industry. He worked for Inland Steel, for I think, a period of something like eight years, back in the eastern U.S. Then, his friend, Bill Draper, invited him out to go to a Big Game, which is of course, the annual football rivalry of Stanford and Cal Berkeley. Pitch came out and stayed with Bill Draper, and they got to talking about venture capital, and Bill convinced Pitch to come out in the early sixties to do that. During the sixties, the kind of start-ups that venture capitalists invested in were principally the type that we talked about before, in computers, and a little bit in communications, and things like that.

Kiley: What were the sources of Asset Management's first fund, which is the fund, I presume, you were assisting Pitch with.

Byers: Yes, the sources of those funds were all his. They were all personal funds by Pitch. Pitch preferred, at that time, to just invest his own capital. It's an interesting perspective to keep that back in those days, companies were started with a first round investment of a million dollars. Usually, four or five venture capital firms would come together in a syndicate to put together that amount of capital for the start-up. For a venture capital firm to invest \$200,000 was sufficient to be a player.

Kiley: That would be consistent with Tom Perkins's own testimony to that effect that his first investment, under the rubric of Kleiner Perkins, in Genentech, was precisely \$200,000.

Byers: That's right.

Kiley: You remained with Asset Management for approximately five years?

Byers: That's right. Pitch and I worked in an office in Palo Alto. We had a great time. We did some good investments together. Qume Corporation was a company begun in the mid-seventies that revolutionized computer printing. Up to that point, printing was either done by large electromechanically complex refrigerator-sized devices. Or on a desktop, they were done by the IBM typewriter printer style which was a ball that revolved around and had raised letters on it. Qume pioneered the daisy wheel printer, it was so called. That one went well for us.

And then, in 1975, I had developed a friendship with two associates who were at the venture capital firm Kleiner Perkins which had begun in 1972. Those two associates had decided to leave and start a new computer company called Tandem Computers.

Kiley: What were their names?

Byers: Jim Treybig and Jack Loustaunou. They had known Tom Perkins because they worked for him at Hewlett-Packard, when Tom was the general manager of the computer division there, prior to starting Kleiner Perkins in 1972. Through my friendship with Treybig and Loustaunou, I did a bunch of homework on the idea of Tandem Computers, and NonStop Computing and convinced them that they should let Asset Management invest in their start-up. Of course, having sprung out of Kleiner Perkins' offices to incubate Tandem Computers, Tom Perkins felt as though that this venture was one that he had control of. So he invited me to come over to his office one day, and share all my homework and diligence with him about NonStop Computing and the viability of this idea, and so on, and I did. He said, "Okay, well, all right, Asset Management can have a piece," and

we decided that Pitch Johnson obviously, being the senior partner, would go on the board. That investment worked out very well. That was how I got to know Tom Perkins.

Kiley: Did there come a time when you left Asset Management and joined with Tom at Kleiner Perkins?

Byers: Yes, in 1977, it became apparent to me that venture capital was going to go through a huge transition as a profession and as a business. That was that it was going to become institutionalized. Because I saw that the pace of technological change was accelerating, and that it was going to take more capital to build companies, and that companies were going to grow at a more rapid rate. All that means is that they were going to need more capital to get started and for rapid expansion as a private company before they could raise capital through a public offering. I also saw that there were changes being proposed in E.R.I.S.A. and in the pension fund laws to allow pension funds to invest in venture capital firms, and so I saw that large pools of capital would be formed over the next few years. I talked with Pitch about raising a fund of outside capital and he chose that he didn't want to do that, that he was enjoying the business model he had at the time.

About that time, I was approached by Tom Perkins to come join Kleiner Perkins and raise a large fund, along the lines I just described. And so, with a feeling of bittersweet and a lot of loyalty to Pitch—I was going to stay with Pitch, but it's typical of Pitch, that he acknowledged that maybe it was time for the apprentice to move on and go on out and seek my career on my own. I am very appreciative to Pitch for the training he gave me, and then, like a father, giving me the freedom to move on. In 1977, I came over and joined Kleiner Perkins. About that time, Frank Caufield joined also, and the firm was renamed Kleiner Perkins Caufield & Byers.

Kiley: Were the four of you the only venture capitalists in the firm at the time?

Byers: Yes.

Kiley: Bob Swanson, the founder of Genentech, had previously been an employee of Kleiner Perkins. When did you first meet Bob?

Byers: I met Bob about two years prior—around 1975. Bob was formerly an associate with Citibank Venture Capital in New York City, and had come out to San Francisco to join Kleiner Perkins as an associate partner, and worked in the offices in San Francisco. Bob had an apartment in San Francisco. While I was working for Pitch, I got to know Bob, both professionally and socially, as a friend. We both joined a tennis group of young people in the San Francisco area, and I decided I wanted the experience of living in San Francisco. So even though

I was working in Palo Alto with Pitch, I moved up to San Francisco and shared an apartment with Bob in Pacific Heights.

Kiley: That would have been about 1976?

Byers: Yes.

Kiley: Which happens to be the year that Genentech was formed.

Byers: That's right. While I was a roommate with Bob, I was commuting down to Palo Alto, working in venture capital on computer start-ups, and things like that. Bob, while working at Kleiner Perkins, became intrigued by some new breakthroughs in science, in molecular biology, specifically recombinant DNA, and in and around the discoveries of Cohen and Boyer. So, Bob started working on the idea of incubating—starting himself from scratch—a young company to work in this field, to be located down in South San Francisco. I benefited from being a roommate of Bob during this period, and started reading some of the books that he had around the apartment, and reading drafts of his business plan, and meeting some of the people he was interviewing to join the company. While we were roommates, he actually got initial funding from Kleiner Perkins, and sprang out of the firm to start the company. An even larger number of people started flowing through the apartment, visiting. These were scientists from Southern California and Boston and Italy and so on.

All of this obviously had a huge impact on me and I think was pivotal in awakening in me a vision of bringing together my love of science, my love of start-ups, and—going back to that epiphany I was describing that I had in the late sixties at Stanford University—of wanting to take a world view and do something for the greater good, for the good of society, and being able to do it within the craft of my own profession.

Kiley: Tell me the people you remember meeting as they were being interviewed by Bob Swanson as prospective employees of Genentech? Who were the people that passed through from various countries around the world, if you can recall their names?

Byers: I don't think I can recall their names specifically. I think there may have been Roberto Crea, who came from Italy.

Kiley: From Reggio di Calabria?

Byers: Excellent! Along the way, I met Herb Boyer, I think at one of the Christmas parties Bob and I threw in our apartment. I'm trying to recall the first time I met you.

Kiley: I believe that would have been in connection with your having founded Hybritech along with Ivor Royston, a subject we'll turn to later in this discussion.

Byers: In 1978, okay.

Kiley: Yes. So, what did you understand Bob Swanson's vision to be when first you heard it?

Byers: Well, we were reading books in the apartment like *The Double Helix* and *Fundamentals of Biology* and things like that. We would have these wide ranging discussions about what is our goal in life, and what do we want to do, and what are our objectives, and so on. Bob clearly had a very big vision, that he wanted to do something that was revolutionary. I remember him stating something that I found astounding at the time, that he wanted to start what would become a major pharmaceutical company.

Kiley: Why did you find that astounding?

Byers: Well, because it appeared to be an industry that was rooted in hundred-year-old history, in most cases. Merck, Lilly, so on, were all founded out of apothecaries or pharmacies a long time ago. If we look in Europe, Bayer and Ciba-Geigy were all founded on chemical bases revolving around large chemical companies. The only example of a fairly recently started pharmaceutical company was Syntex, down in Palo Alto, which had been started in the 1950s.

Kiley: In fact, no new pharmaceutical company that I know of had been started since the 1962—was it?—revisions to the Food and Drug Act that raised the bar for approval of human therapeutics.

Byers: That's right. What we knew at the time was that the FDA was very cautious. The general business idea of launching a new venture to go into the pharmaceutical business, around risky new science to overcome what appeared to be huge regulatory hurdles, and then go into a competitive market against powerful large companies seemed like a—

Kiley: A daring thing to do.

Byers: Very daring, yes. [Laughs]

Kiley: The founding notion of Genentech was to use recombinant DNA to produce copious quantities of human recombinant insulin. Were you aware of that, and if so, when you first heard Bob propose that, did you have the view whether that could be pulled off?

Byers: Oh, I don't think I knew enough to have an informed judgment about whether or not it was a good idea. He talked about insulin, he talked about human growth hormone, and somatostatin. These were all fairly foreign words to me at the time.

Kiley: Had you studied biology of any kind in your undergraduate days?

Byers: None at all.

Kiley: Can you describe the circumstances in which you and Bob were living at the time? You mentioned that it was an apartment in San Francisco. I imagine it might have been like many apartments inhabited by young men, emphasis more on function than fashion. Would I be correct?

Byers: Yeah, it was pretty spartan. Neither one of us had any skills at arrangement or decoration. It had a nice view of the San Francisco Bay. We were sharing an apartment out of economic necessity because it allowed us to afford to live in San Francisco, in an apartment, and that's not changed to today, I hear. The living room was pretty basic, with a couch or two. The dining room had nothing in it but a ping pong table. When we entertained, we would just cook a big pot of spaghetti, and have everyone sit around the ping pong table and eat off of it. It was all we needed at the time.

Kiley: By the time you joined Kleiner Perkins, Tom Perkins had made his initial investment in Genentech. Subsequently, you led the firm's investment in Hybritech. Do you recall any other life science investments made by Kleiner Perkins, prior to the Hybritech investment?

Byers: When I arrived at Kleiner Perkins in December 1977, they had both the Genentech investment, and they had made an investment in Cetus, a company located in the East Bay area of San Francisco metropolitan area. I don't recall much about what Cetus was at the time. I think it was a company pursuing a lot of technologies.

Kiley: Do you recall if Kleiner Perkins invested in subsequent rounds of Cetus Corporation?

Byers: I don't. I don't really remember anything about that. I think what happened is, that Tom Perkins had the firm sell their position in Cetus to avoid any potential conflicts of interest, because it looked like Cetus and Genentech might end up competitors. So Cetus was not anything active that we worked on when I was there.

Kiley: How long did you continue to room with Bob Swanson?

Byers: Oh, I think until 1978 or '79, something like that.

Kiley: So you were able, vicariously to follow Genentech's growth through its early years.

Byers: Yes, and it was a marvel to watch because I think we all look back on the founding of Genentech now, and see it as a model that we still, to today, want to replicate because it had features about how it was put together that have stood the test of time. Obviously, Genentech went on to be a great success too. Those features are that it was started with a modest amount of capital, to prove something first—to prove a scientific principle, and that's what we now call the "proof of principle set of experiments." The way it was done was to define what is the most important risk of this venture to be overcome, and to put all the initial dollars behind that, and that's exactly what Bob did. Bob funded some research projects in various labs to see if proteins could be made from recombinant DNA technology and in proteins of commercial interest. That proved to be right.

So, being around Bob and being in Kleiner Perkins and watching Bob and Tom Perkins develop Genentech inspired me. Because I was at Kleiner Perkins, the idea of developing more biotech companies was acceptable.

Kiley: That is the end of tape 1 side A.

[End Tape 1, Side A] ##
[Begin Tape 1, Side B]

Kiley: Side B of the October 4 interview with Brook H. Byers.

Brook, what was the first life science venture you were involved in, personally, once you joined Kleiner Perkins commencing in 1977?

Byers: It was Hybritech. I joined in December 1977 and started performing work to screen investment proposals that came into the firm—most of them in computers and semiconductors and the usual kind of start-ups that venture capital firms were seeing at the time. Bear in mind that even though Kleiner and Perkins had in 1976 funded Genentech as a start-up, there were really no other biotechnology start-ups being formed. I think a lot of entrepreneurs and scientists and venture capitalists were taking a wait-and-see attitude on this strange new field called recombinant DNA and biotechnology. Many people back at that time thought that both Bob Swanson and Tom Perkins and the Kleiner Perkins Caufield & Byers firm were a little bit out of our minds to be taking so much scientific risk in an unproven industry.

Kiley: Was there also concern about the then controversial aspects of recombinant DNA?

Byers: That was still in the air, yes. There had been the Asilomar conference a couple of years before. The R.A.C., Recombinant DNA Advisory Committee, had been

formed and was operating to make sure that this new science was not going to have ill effects on the environment, or medicine, or society. That was another element of risk, besides all the ones that I mentioned before, about building a new business in this industry.

Around May of 1978, I received a call from a scientist at University of California, San Diego, named Dr. Ivor Royston. He described to me an idea he had to start a new biotechnology company. He, on the phone, drew a parallel with Genentech. The reason he did was that he admired what our firm had done in taking the risk to invest in Genentech, and he proposed the idea of starting a new company to work on monoclonal antibodies and asked if I would meet with him. We met in May of '78, two weeks later, after he flew up. We had lunch in San Francisco, and Ivor described to me some inventions that had taken place in England, just a year or so before, at Cambridge University, where Drs. [Georges] Kohler and [Cesar] Milstein had developed a technique of making hybridomas and producing monoclonal antibodies.

Now up to this point, all antibodies that had been produced were made in a polyclonal way, that is, animals were injected with an antigen of interest, and then the animals would produce an immune response. The animal's serum was taken and the antibodies would be separated out. There were large animal facilities around the world to do this kind of thing. The idea of a monoclonal antibody as a pure reagent was a startling idea. Ivor's startling idea was to start the first company to go after this.

Well, this was just the thing I had been looking for, because I had been curious about the whole biotechnology industry, had been inspired by Bob Swanson, I was working in a firm that had the nerve and the willingness to take risk to invest in a biotechnology start-up. I felt as though I was, by destiny, in the right place at the right time. But of course, I didn't know anything about this science, so I started off on a path of diligence, and trying to learn as much as I could. That went on for five months before we funded the start-up.

Kiley: Generally speaking, is it important in founding biotechnology or other venture capital business to have some prospect of patent protection for the fruits of research?

Byers: Oh, yes.

Kiley: It was my understanding that Kohler and Milstein themselves had not patented the hybridoma technology that gave rise to monoclonal antibodies.

Byers: That's right, they had not. That was a curiosity to us, because it seemed like a huge invention. The best we could tell from articles and Ivor networking in the scientific community, which of course is one that is very open in communication

worldwide, was that it was almost a policy decision by the M.R.C. [Medical Research Council] in England that it was not going to patent that invention.

Kiley: Did you have a view of whether what Ivor proposed to do with monoclonal antibodies would itself be protectable by the new company?

Byers: Well, we didn't know that at first, and it was a fundamental question for us because if we had taken all of the risk of starting a company and hiring employees who were going to bet their careers on this, and investing capital in this new idea, would we develop any product that was protectable by patent so that it would justify the three to five years it would take to bring a diagnostic product to market, and if we were lucky enough to develop a therapeutic product—the eight to ten years to do that—would there be a reward at the end? Or would we be doing it all to be shared by larger competitors?

So, part of the diligence process was that throughout the summer, we did our scientific diligence and learned as much as we could about the diagnostics industry and interviewed various potential management members and were learning as much as we could. In the fall, I talked to Bob Swanson about who he used as intellectual property advisors and counsel. He put me in touch with Lyon and Lyon—a firm in Los Angeles that had some talented partners.

Kiley: I have in mind that hybridomas are living cells. As I understand it, hybridomas would be, if you will, the living factors that would produce monoclonal antibodies. Had you any concern over the question whether these living cells could be patented as of 1978 or 1979?

Byers: I don't remember that my thinking was that sophisticated at the time. I think we were hoping that we could perhaps patent the hybridomas or perhaps patent the monoclonal antibodies, but patentability and intellectual property is complex and enough of an art and a science itself that I was going to rely on the expert I could find. I contacted Jim Geriak down at Lyon and Lyon—a very talented patent lawyer—and he became intrigued about the whole project, and assigned to work on it, a young man named Tom Kiley. We then went on to have a series of meetings in San Francisco and down in La Jolla. I took Tom down and introduced him to Ivor Royston.

Kiley: You may refer to me as myself, or yourself.

Byers: [Laughs] Okay.

Kiley: So you mentioned diagnostics. Had you given any thought in 1978 to the use of monoclonal antibodies as therapeutics? And if not, why not?

Byers: We had a vague notion about that, at the time. We liked that fact that the diagnostics applications would have a shorter FDA approval process. The idea

of using an antibody as a therapeutic, of course, was known, because there were therapeutics at the time that were polyclonal. The most obvious of those was hepatitis antibody which is given to provide three to six months protection against hepatitis for people who might go into exposed areas and so on like that. Horse antibody, I believe was the source given for rabies after exposure and things like that. People having immune reactions to those, that's usually what's the toxicity for those kinds of therapies. So, we had the theory that well, if we could produce a monoclonal antibody, it would be pure, and it might have less reaction and less other biological components. Of course, the source of all of this was going to be from mouse hybridomas—so still not human species. It was a dream of ours, but it was not the prime founding basis.

Kiley: By whom was Ivor Royston employed in those days?

Byers: He worked at University of California, San Diego. He had a lab there and a lab at the V.A. Hospital.

Kiley: So a joint appointment, so far as you know?

Byers: Yes, and he was a practicing oncologist, also.

Kiley: Did he have any partners in the formation of Hybritech other than yourself?

Byers: Well, he did, and we were very fortuitous. The founding of companies depends on so many elements to come together, in just the right way and the right time. Of course, one of the most important elements is the people side of things, because science is good, but it's not worth much without implementation by the right people. Starting a company is an art and requires certain personalities too. There was a young lab manager, working in Ivor's lab at UCSD, named Howard Birndorf, a master-degreed scientist who had a real entrepreneurial streak, and was ready to leave UCSD, and join the new company, and Howard did. He became employee number one.

Kiley: What are the characteristics of an entrepreneurial streak? How do you recognize that? What do you see in someone who is so "streaked"?

Byers: I define the streak as somewhat irrational and rational complements. Howard, I think, embodies, in my mind, the classic entrepreneur. He did when I met him and he still does today, six companies later. Howard is passionate. He is smart about science. He has a nose for opportunity and how to turn science into products. He has a driving sense of urgency and does not let people or obstacles get in his way. He has a kind of a clarity of vision about what needs to be done. He's the classic starter.

Kiley: As long as we're on Howard, why don't we see how many of those six companies you can remember. Can you list them?

Byers: Well, let's see if I can, because every one that he started, Kleiner Perkins Caufield and Byers has invested in, and I've been on the board. That would be— Hybritech is the first. Then Genprobe, Idec Pharmaceuticals, Gensia, Ligand Pharmaceuticals, and Nanogen.

Kiley: All right; each of those companies became a public company. Several were acquired and the others continue to excel. We'll spend more time on these down the road, but Genprobe was another diagnostics company, was it not?

Byers: It was. It was a company that spun out of Hybritech. In 1984—

Kiley: Let us not get too far ahead of ourselves. I just wanted to characterize the companies. Idec Pharmaceuticals, of course, is very valuable pharmaceutical company on the strength of its lymphoma humanized monoclonal antibody treatment. Tell me in what business Gensia engages.

Byers: Gensia was started in 1986 to do drug discovery and development for cardiovascular applications of biological and small molecules.

Kiley: Ligand is another drug discovery company?

Byers: Yes it is, working on biological targets, principally out of the lab of Dr. Ron Evans at the Salk Institute, working on intracellular receptors.

Kiley: And Nanogen is a laboratory on a chip?

Byers: Yes, it is. It is what we call today, a microarray chip with genetic markers.

Kiley: So, at some point, I will solicit your assistance in getting Howard Birndorf to agree to talk about the evolution of biotechnology, as he seems to have touched many bases. Let's come back to Hybritech. You were the founding CEO of Hybritech?

Byers: I was. In October, we decided to go ahead and launch the company and with a sign off of yourself, on the intellectual property freedom to operate, and your view of the attractiveness of this, and input from Bob Swanson, that he thought it was a good idea, and not competitive with Genentech, and all the other diligence we had done, and bear in mind, in comparing the diligence we did on starting Hybritech to the kind of diligence we do today, it was pretty scarce. First of all, there weren't many people to talk with, because not many people were in the biotechnology industry. That is, other than the ones in Genentech we knew, we didn't know anyone in the pharmaceutical business, in our personal networking contacts, compared to the hundreds we know today. Our knowledge base and perspective was pretty meager. I think we were quite naïve and quite lucky in how things went. We put in \$300,000 as initial start-up capital into Hybritech. Just as we had done at Genentech, we defined a project that they

needed to accomplish. That was—we gave them six months to produce a monoclonal antibody to hepatitis.

Kiley: Before we get further into that, tell me if it was unusual for a founding venture capitalist to become an officer of a new company.

Byers: Well, it was, and still is today. Rarely does a venture capitalist go in as acting president and founding CEO of a company. Venture capitalists, I think, rightly prefer to invest in full management teams if they can, but of course, that's a luxury that's rarely available. Sometimes, fully formed teams in a start-up is not the right thing anyway, because they might form because they feel as though they need to fill in all the boxes, when in fact, sometimes the best way to start a company is just with the scientists and the people who are going to work on removing the technical risk. The kind of people that can be hired later down the road when that risk is removed are much more qualified. But to get back to your question, no, it's rare. I think it's particularly rare because people who go into venture capital, for the most part, do it because they love to coach and advise and be an active board member, perhaps, but not to manage something.

In the case of Hybritech, we wanted to start the company, and there was no one to be president. Howard Birndorf looked like a talented scientist, but had no experience in managing anyone. I had no experience in managing anyone, but perhaps my best qualification for the job was that I didn't want it long term. My first assignment was to go find a president. So sometimes, in starting companies, taking and holding a title until the right person is found is the smart thing to do.

Kiley: Did Ivor Royston give consideration to leaving his university position to become a full-time employee of Hybritech?

Byers: No, he wanted to stay at UCSD and we respected that. Ivor had multiple appointments there as we mentioned and was a practicing oncologist, and I think, saw as his role model, Herb Boyer at UCSF, who stayed at that institution, and was a consultant to Genentech.

Kiley: In those days, were there impediments to the people from the academic community going commercial, if you will?

Byers: There was suspicion. It was sort of like when Bob Dylan went electric in the sixties. It was controversial. People were wondering, what's up with that, and will bad come of this? Ivor, I remember had to suffer indignation and suspicion from his colleagues on campus, and he would tell me about that. We would have dinner once a week and go over plans and it was something we had to console him on. Because remember at that time, this was all new. The only other model in the U.S. was Genentech, and that was, although in the same state, eight hundred miles away. With Ivor, we were seeing him as a pioneer, but his colleagues in academia were seeing him as a turncoat.

Kiley: So it took a certain amount of courage on his part, and on Boyer's part, to participate in the formation of these companies.

Byers: Oh, yes. It's hard for us, today, seeing a vibrant biotechnology industry worldwide, where in the U.S. alone, there are some eighteen hundred biotechnology companies, all of them having consultants or founders or advisors or board members from academia, to think that it was that way, but I suppose this is the way a lot of revolutions begin.

Kiley: Clearly there's been a paradigm shift in relations between industry and academic science in the life sciences over the last twenty years or so. At the outset you say there was suspicion, there were fears. To what extent have those fears been realized and to what extent have they proven illusory? What is your view of the current health of the industry-university relationship in biotechnology?

Byers: I think it's all turned out fine. I think it's for a variety of reasons. One is, I think the industry participants have all behaved well—have all shown a great respect for the intellectual property developed in universities and academic centers. We and industry have helped those universities develop good offices of technology licensing, along the way. There was a lot of learning to be done, on both sides. From those early days of licensing intellectual property out of UCSF and Stanford, in the case of Genentech, or UCSD, in the case of Hybritech. I think the academic institutions have learned and grown along the way. They've had fits and starts about conflict of interest rules, and so on like that, but I think everyone has developed it well, and to think that a whole industry has grown up in only twenty-five years—that's a short time in terms of huge industrial revolutions, I think—there has been relatively little problem.

Kiley: You mentioned earlier that as a proof of principle, you challenged Hybritech to produce a monoclonal antibody to, I presume, hepatitis B surface antigen, within six months. What did that take, and was it achieved?

Byers: Well, the first thing we needed to do was to set up an independent lab of the company's own, because obviously, it was going to work on developing this science for its own benefit, so it could not work on the university campus.

Kiley: Did you give consideration to that and were rebuffed by the university?

Byers: No, we just decided to go set it up on its own, and set Howard to the task. He proved his entrepreneurial streak early on by me saying, "Well, listen, find a lab and call me a couple of weeks." Two days later, he called me and said he had rented a lab. It was a couple of rooms at the La Jolla Cancer Research Foundation, which was located on Torrey Pines Road in La Jolla. He invited me down to visit, so I flew down the next week, and was quite astonished to see that he already had the lab set up and outfitted, and was prepared to hire the first scientist, Gary David. So we set out a schedule of this challenge I put to him,

within a three hundred thousand dollar budget, to produce a commercial grade monoclonal antibody as defined by various scientific parameters and measurements. The remarkable thing about Howard is that they did it in three months.

Kiley: Did he lease the laboratory space before you put dollar one into Hybritech?

Byers: I think it was all set up and happened at the same time.

Kiley: At that time, Abbott Laboratories was strong in hepatitis diagnostics, as I recall. What thought did you give to potential competition when you agreed to put seed capital into Hybritech?

Byers: Well, we had looked at what we could find out about Abbott. Now back in those days, there were no industry newsletters, no analysis of the industry, diagnostics or therapeutics. There were none of the source materials, resource materials, weekly *BioWorld* or *BioCentury* newsletters to read.

Kiley: No Internet.

Byers: No Internet, none of that existed. No Google search engines. Nothing.

Kiley: Kleiner Perkins would create all that later, right? [Laughter]

Byers: [Laughs] Yes, to serve our needs and others. So we were naïve. I think if we had known everything about all the potential huge competitors, we might not have even done it. One of the benefits we had, I suppose, was some combination of naiveté and ambition and this desire to do something on our own.

I think we had this fundamental principle in mind, that if we could make a pure reagent, if we could make monoclonal antibodies that had a purity of their biological mission, and better binding affinity characteristics and so on, that it would even make for a better test. How the business model would play out, I don't think we had a very clear idea in mind.

Kiley: I'm struck by the fact that Genentech set out to make larger quantities of more pure protein therapeutics, and Hybritech, using the hybridoma technology was going to make large quantities of more pure monoclonal antibodies. Tell me whether in the late 1970s, you or anyone around you held a larger vision for the life sciences than the production of more or better proteins.

Byers: In the late 1970s, I think we knew that this would be big because it would be applicable across the whole range of biological activity. By that, what I mean is, that the complexity of the human body involves a large number of secreted proteins, cell surface proteins as targets for therapy, and obviously, there are a huge number of diseases and disease states and things to be measured, so the

enormity it seemed to us was the complexity of the human biological system. We felt there would be a lot of amplitude of opportunity, and that if we just did this one thing right, we would find our way.

We did not have the business model mapped out, or the ultimate value proposition mapped out, which are all things that we do today, in doing a start-up, we're much more sophisticated, let's say. We have much more information at our disposal, and we have much more experienced management who are quite willing to join a small company. Back then, we didn't have any of that. We just had something that was available then that is not available today, and that is, a wide open frontier. I think there was a feeling of a green field, and that we were the first. We had decided to start the first company, in either recombinant protein or monoclonal antibody, and that we didn't know all the answers, but we had time to figure it out, and the opportunities were huge. There was not a sense of any competition because we asked around at scientific meetings, and so on, "Are any large companies poking around in this area"? and we didn't hear of any.

Kiley: By doing this one thing right, I assume you're referring to the hepatitis diagnostic.

Byers: That, and beyond, because hepatitis was just the first proof of principle, but then we were going to go on, and we started to build a list of antigens that we wanted to make monoclonals to.

Kiley: Did you ultimately make monoclonals to the antigens on that list?

Byers: Yes.

Kiley: At its peak and before its acquisition, how many different monoclonal antibodies were produced at Hybritech if you recall?

Byers: Oh—

Kiley: Referring to antibodies against different antigens.

Byers: Oh, dozens.

Kiley: Ultimately, did Hybritech develop its own proprietary position?

Byers: It did. As it turned out, I think the strongest proprietary position it developed was on the format of the test that was used for diagnostics.

Kiley: Referring to the Tandem immunoassay?

Byers: That's right—the idea of using two antibodies, which was something that had not been done before.

Kiley: Indeed that was patented by Hybritech in the United States, was it not?

Byers: It was.

Kiley: Did there come a time when competition arose?

Byers: Yes, well, once a pioneer proves out a good idea, or course, others want to copy it. Two ways of copying: there's, one, license it and make it: or just go ahead and copy it and go into market and competition. That happened. There were some companies who adopted that format, once they saw that it could be done, and there were a bunch of legal challenges that went on through the eighties.

Kiley: Turning to the first alternative, did Hybritech license its technology to other companies? Or was its founding vision, to make and sell diagnostic kits for its own account?

Byers: Oh, it was to make it for its own account. It wasn't to have a licensing revenue model, it was to make and sell. And so, it had to protect its proprietary position.

Kiley: Was there any thought that if you had a surfeit of riches, more than you could handle, you would license to third parties?

Byers: Yeah, I think that's always considered by a company.

Kiley: But only ancillary to the main purpose of a full line of diagnostics?

Byers: Yes.

Kiley: Is a full line of diagnostics important to successful competition in that industry?

Byers: Yes, if it can be sold by the same sales force. Speaking generally, I think, if a company is going to build a sales force to sell something, if it's diagnostics, or if it's therapeutics, or whatever, it wants to use its scientific resources, its intellectual property position, to build a portfolio of products, to put through that same distribution channel.

Kiley: When did Hybritech become a publicly owned company?

Byers: Oh, I think it was like 1981.

Kiley: A year or so after Genentech's own successful offering?

Byers: Yes.

Kiley: How many were employed by Hybritech at the time it went public?

Byers: Well, I'm guessing here, but I would think it's on the order of something like a few hundred.

Kiley: Where did Hybritech stand in developing its products toward the marketplace at the time of its IPO?

Byers: It was still early. It's not as though the company was profitable, based on product sales.

Kiley: Was it selling anything?

Byers: I think it was selling some antibodies as research reagents at the time.

Kiley: You mentioned that a time came when other companies, in your view, adopted Hybritech technology and began to compete. Who were those companies?

Byers: There was a small company in northern California, Monoclonal Antibodies, Inc., I believe, and Abbott Diagnostics, and there may be some others I don't recall.

Kiley: I recall that litigation ensued. Who sued who?

Byers: I don't remember all that. I literally don't.

Kiley: I will recall just for the record that there was litigation between Hybritech and Monoclonal Antibodies, in which Hybritech was represented by my one-time law firm of Lyon and Lyon, and in which Hybritech's patent position was vindicated, and Monoclonal Antibodies left off competition.

There came a time when Hybritech was acquired by another company. When was that?

Byers: Yeah, I believe it was in 1986.

Kiley: How long did you remain active in the management of the company, or as a director of the company?

Byers: I became president of Hybritech when it was founded in October '78. Once we had done the proof of principle, we felt we had something to show to a presidential candidate. I was networking and looking around for someone, and I heard that there was a young executive at Baxter's division, up in Orange County, California, who was thinking of starting a monoclonal antibody company. I called him up and told him a little bit about Hybritech, and we agreed to meet. As I recall, I drove up from San Diego, because I was commuting down to San Diego to work three days a week at Hybritech, and then come up and working two days a week at Kleiner Perkins.

Kiley: Double-dipping.

Byers: [Laughs] Never sleeping. And so, I drove up, and Ted Greene drove down from Orange County and we met and had lunch, and shared a big vision of the two of us. It was perfect timing because he wanted to leave Baxter and start a company and run it himself. He was what I was looking for. He had a good knowledge of the science, he had worked at the Hyland division of Baxter, which made reagents and components. He joined the company in the spring of 1979, and he remained CEO of it until it was acquired by Lilly in 1986. When Ted joined the company, I became chairman of the board and remained so until the acquisition by Lilly.

Kiley: How did the company come to be acquired by Lilly, and why?

Byers: Well, in 1986, we realized that if we were going to further develop as a company, we were going to need very large amounts of capital. Also, we wanted to expand the programs. Hybritech had a wealth of talented R&D employees, had a lot of projects that it was working on, and wanted to expand that. In order to do that, it needed more capital, a kind of a broader base from which to work. We decided that even though we're a public company, it was, given the markets at the time, going to be hard to raise the amount of capital we needed. So, we looked around to be acquired by a larger company.

Kiley: Lilly was among them, obviously, among the companies that you considered. Was Lilly, at that time, a player in the diagnostics business?

Byers: No, they weren't but they thought that they would want to get into it. They saw, perhaps, a tie between diagnostics and therapeutics. We talked to all the usual suspects at the time, and they were the ones who showed the most interest.

Kiley: What has become of Ted Greene?

Byers: Ted has gone on to be a venture capitalist, and an entrepreneur in San Diego, and set up his own venture capital operation, was very successful at it, and also ran one of his ventures for a period of time too. I think he's still doing that in San Diego.

Kiley: Let's go back a little bit in time to 1980, when Genentech went public. By then you were an employee, perhaps a principal of Kleiner Perkins, I can't recall. Do you recall that day?

Byers: Well, yes, because, it, I think, was so remarkable, that here was a company that we saw from the beginning, so we saw it from the inside out. Up to that point, for a company to go public, it needed to have sequential quarterly financial results that showed good revenue growth and profitability. And here was a high science company, most people reading the prospectus probably didn't

understand the science, and it was this whole new paradigm, this whole new industry. It was the first biotech company to go to public market investors. I think no one knew how to price it as an IPO. Sitting here today in 2002, we can look back on the past, even in recent five years, and see IPOs that were priced in the teens and shot up to high prices and so on, during what we now call the bubble. Back in 1980, nothing like that had ever occurred. This was a shocker, and pleasantly so, for everyone. I think it was priced in the teens and went up to eighty-nine or something like that that day. It was always referred to, for decades after, as the Genentech phenomenon.

Kiley: How was Hybritech valued when it went public, do you recall?

Byers: It didn't have as spectacular a IPO, but I think Hybritech probably could not have gone public if Genentech's IPO the year before had not gone so well. The spectacular first day rise of Genentech stock was fascinating, but of course what matters in the long run is the sustainability of the market valuation, stock price, and the stability of that, for investors to have predictability.

It held its own, and so I think, provided some sort of base of comparison or belief, so when the Hybritech IPO came along, we talked to investment bankers, and the esteemed investment banking house of Goldman Sachs agreed to be the managing underwriter. They were nervous about it. They had never done anything like this before, but they wanted to stake out a position in biotechnology because they too saw that this was a coming industry, and it was going to be very important.

Kiley: Were they joined by other investment banks in the Hybritech offering, that you remember?

Byers: Yes, Dean Witter was a co-manager of it, as was Paine Webber.

Kiley: And do you recall how the market valued Hybritech?

Byers: Oh, sorry. I think market capitalization might have been around one hundred million dollars. We'd have to look that up, but I think it might be something like that. It was a fraction of what Genentech's was at the time.

Kiley: How did that compare to the evaluation Lilly put on Hybritech when it acquired the company?

Byers: You know, maybe I'm getting these numbers messed up. I don't know what the evaluation was on the IPO. The hundred million was the base price Lilly paid, plus Lilly put warrants into the arrangement. It was very complex because people could take cash or they could take a convertible from Lilly, and they got warrants too. The shareholders got warrants too.

Kiley: Is that another way of saying that even Lilly in those days was having difficulty figuring out how to put values on new life science companies?

Byers: Yes. Yes, I think it was very hard for everybody. The interesting thing is, during the negotiations with Lilly, there was a back and forth. Lilly was going to use stock, then they were going to use cash, then stock, then cash, and they ended up using more of a cash structure and instruments, but they wanted the employees and the shareholders of Hybritech to feel as though they were part of Lilly, and an owner of Lilly, so warrants were added to it. At the end of the day, the warrants were worth more than the cash. The whole value, over the next five years or so, added up to almost a billion dollars.

Kiley: So, by the 1981 IPO of Hybritech at a minimum, and the same thing can be said with greater reason because of the subsequent valuation of Hybritech, Kleiner Perkins had two solid life sciences wins. What's your recollection of the next life sciences investment Kleiner Perkins—by now, Kleiner Perkins Caufield & Byers—makes?

Byers: Well, the IPO of Hybritech in 1981 certainly helped my career because it showed that I could incubate a company, and shepherd it along, and it would go on and be an early financial success, and the company was interesting and developing good products. I was emboldened to go out and do more in this field of life sciences, and—

[End Tape 1, Side B] ##

[Begin Tape 2, Side A]

Kiley: First session of the interview with Brook Byers, tape 2 side A. We're resuming October 4, at 11:30 a.m.

Brook, before we talk about the additional investments you were emboldened to make in biotechnology as a result of the Hybritech success, I want to a little better understand your own early role in Kleiner Perkins. As I understand it, Kleiner Perkins was still operating from the first fund it had raised at the time you joined, is that correct?

Byers: Yes, that was called just Kleiner and Perkins, raised in 1972.

Kiley: How much did Kleiner Perkins raise?

Byers: Eight million dollars. At that time, it was the largest venture capital fund in the world.

Kiley: My goodness. And you became a principal in the second fund, did you not?

Byers: That's right. We called it Kleiner Perkins Caufield & Byers I, raised in the spring of '78.

Kiley: All right. During your earliest years at Kleiner Perkins, how did you and Tom Perkins interact?

Byers: Well, he was my second mentor. I count Pitch Johnson as my first, and Tom became my second. In that way, I think I am, probably, the most fortunate of almost anyone who has ever been in venture capital. I've had two of the great venture capitalists as mentors. When I joined the firm, of course, Tom was on the board of Genentech, and he and I would spend time talking about the progress of that young company. When I came to Tom with the idea of Hybritech, after spending two months with Ivor Royston talking about it, Tom was very encouraging. because he had been working with Genentech, had a view of biotechnology, you know, had a vision for it. I think, if I had been in any other venture capital firm in the United States, Hybritech probably would not have happened. So, Tom was my mentor, and kind of my partner in it. When we invested in Hybritech, both Tom and I went on the board of directors, and worked in a collaborative way on it.

In the early eighties, I had a sense that this biotech industry was going to broaden, and become substantial, and also, that I wanted to do more life science ventures. I did an investment in a start-up for KPCB I, named Caremark, in 1979. This was around an entrepreneur in Orange County, in southern California, who was coming out of Baxter, and wanted to start a company to serve patients at home who needed total parenteral nutrition. This was a service business that did have some technology component, and pharmacy, and the mixing of these IV solutions for the patients. We got involved in that, and I went on the board of directors of that. That broadened my interest in the whole healthcare field, and helped me, actually, to become a better biotech investor on down the road, because it was a step that broadened me into understanding medicine, the medical field, and looking at disease and disease treatment, in a broader context.

Kiley: Who was that entrepreneur?

Byers: That was Jim Sweeney.

Then in 1981, we had the opportunity to invest in a second round of Applied Biosystems. This, of course, was the important company that was started out of technology from Lee Hood at Caltech. The company was started up in Foster City, and its goal was to develop an automated instrumentation for working with DNA and peptides, and so on. It was something we instantly gravitated to, because of the experience we had had then at Genentech and Hybritech. Applied Biosystems, of course, has gone on to do magnificent work in instrumentation and reagents, and is a basic pick and shovel, used by every lab in the world, in

biological sciences. By this time, about '81, '82, then, we were starting to pick up some momentum at Kleiner Perkins about having a brand of a place to go to, for entrepreneurs who wanted to start something in instrumentation, or medical, or life science, or biotech.

Kiley: Just to complete the record, am I right that Caremark was first called Home Healthcare of America?

Byers: That's right.

Kiley: I think in this time frame, Kleiner Perkins had also invested in a company called Collagen.

Byers: Yes, that was an investment Tom Perkins made back in the same year he made the founding investment in Genentech. Collagen was a company started by some doctors and scientists out of Stanford University.

Kiley: Amongst them, Howard Palefsky?

Byers: He was hired later as the president. It was initially started by some doctors who made the observation that they could separate out and purify collagen from animal sources and use that collagen as an injectable.

Kiley: An injectable for what purpose?

Byers: For some cosmetic applications, and for some repairs of biological functions of the body, like sphincter repair, and things like that.

Kiley: Collagen itself, in time, became a public company, did it not?

Byers: It did.

Kiley: So, that would be another win for the Kleiner Perkins troops. Brook, in these years, you were continuing your education in the venture capital trade, presumably under the mentorship of Tom Perkins, and I gather devoting a great deal of your energies to ensuring the success of Hybritech. What else were you doing?

Byers: Well, Hybritech was important to me, both as professionally and also personally, because it was something I of course had played a role in founding, and it was in my bones. I thought about it every day. Of course, I was in San Francisco, and it was down in the San Diego area, but I was on the phone with them every day, and it was a good close working relationship. I was involved in recruiting all the management that came in. We eventually built one of the best management teams that has ever been in biotechnology, I believe. We can go into later, what

all those people went on to do, after the Lilly acquisition, and that was start their own companies.

Kiley: I remember Tom Perkins describing to me, once, what he calls the repeater principle, which I gather, has become one of the main strengths of Kleiner Perkins and its ever expanding network, and *keiretsu* members, as I think you've called them. Did there come a time when your partners at Kleiner Perkins resented in any way, your preoccupations with Hybritech?

Byers: No, I think they thought it was rational, because we had a large ownership position in it, and we had also invested in Home Healthcare of America, which was later acquired by Caremark. Both of those companies were in the KPCB I portfolio, and I was on the board of both. That was a relatively small fund, as we look at it today—a fifteen million dollar fund—but at that time, relatively large. A large portion of the capital was in those two, so that was a good thing. I think in terms of most venture capitalists, and how they allocate their time, yes, I was putting a disproportionate amount of time into Hybritech, for the reasons I stated.

But also, I was learning a lot. To me, it was an endless challenge to learn about, not just monoclonal antibodies, but biological science, and monoclonals, actually of course, have to do with the immune system. I was learning about clinical disease, because Hybritech was starting to turn its attention to thinking about therapeutics, as we got into the early eighties. All of this was to lay groundwork for my activities later.

We went on to make an investment in Acuson, which was a group out of Hewlett-Packard's labs that was developing a computed ultrasound system, that was going to revolutionize, in time, ultrasound diagnostics. And, we invested in Cardiovascular Devices, a company down in southern California, that had a blood gas measurement device system; and also, we participated in investing in the Liposome Company, in Princeton, New Jersey, which was working on drug delivery through liposomes.

Kiley: All three of those, as I recall, successfully transited the passage to public ownership.

Byers: They did. And then, in 1983, I took a sabbatical. We instituted such a program here in the firm, because we realized venture capital is an intense and very long term profession. We had heard about sabbatical programs from universities, and thought, what a good way to keep people rejuvenated, and people could go off and do what they wished by doing that. I took the three months to do a lot of travelling around the world with my wife, something I had never the opportunity or ability to do before, took a lot of books with me about science and medicine. While I was travelling in Asia, during that period, reading all those books, I had

what might be called a personal epiphany, that what I wanted to do with the rest of my career in venture capital was really focus on the life sciences exclusively.

Now, this may sound obvious today, since there are venture capital firms that have multiple partners, who do nothing but life science investing, but back in the early eighties, that was considered heresy. It was believed then that venture capitalists were to be generalists, and that the skills we were to bring to each venture were business skills, of hiring and building management teams, thinking through business strategies, and raising money for the companies, and helping them with financial strategies. People did not specialize back then, either in computers, or communications, or biotechnology, or life sciences, or any industry area.

So, I came back, and discussed this with my partners, and I think they thought that something had happened to me on this sabbatical [laughs], that I became infected with something. In fact, yes, I had become infected with something. It was this love of life science that began back when I was a roommate of Bob Swanson's and that infection had now become complete. I asked my partners for their indulgence, Tom Perkins, Eugene Kleiner, Frank Caufield, that I wanted to specialize and focus in this area. I think part of it was that I felt I was incomplete as a board member, advisor, coach to these teams if all I did was talk to them about the general business things. I wanted to go deeper. I wanted to understand the science. I wanted to understand the clinical mission of these companies. I felt that biotechnology had come to the point where starting companies around biotechnology, in itself, was not what we were going to be doing, but we would actually be wanting to start companies around clinical goals, solving specific medical problems, using biotechnology as the platform to do that. I started a process of educating myself.

The first opportunity came in 1984, when a group of two employees who were at Hybritech wanted to leave and start a diagnostics company, in and around DNA diagnostics. That was a very different technology that didn't exist in Hybritech. The technology idea came from a scientist who was in La Jolla. The two employees left Hybritech—one of them was Tom Adams—and started Genprobe, and we had the opportunity to invest in it. I went to the Hybritech management and board of directors and asked them for permission to do this, and they gave it. We went ahead and invested in Genprobe. This was my first test of learning a new science. DNA diagnostics took me into learning all about the internal functions of cells, especially, infectious cells—bacterial and viral infections—because it involved all their mechanisms.

Kiley: Who was the other scientist, beyond Tom Adams, who left Hybritech?

Byers: It was Gary David, who had been a founder of Hybritech.

Kiley: I believe you said he was the first scientist hired by Hybritech.

Byers: Yes.

Kiley: You mentioned a La Jolla-based scientist, whose ideas were seminal. Do you recall his name?

Byers: I don't.

Kiley: All right. The new company was to be called Genprobe?

Byers: Yes.

Kiley: Was that solely a Kleiner Perkins investment, or did others participate in the first round?

Byers: I think that there was another founding investor. It was CW Ventures, and the board member was Chuck Hartman. We then made one more investment in Interpore, which was a company that used synthesized material to do implants for bone reconstruction. That was more of a crossover between biology and medical device. Then, in 1985, I took most of the year to do a lot of homework and survey studies about disease needs. What I was doing at that time, then, was looking at what are the major unmet medical needs of society that needed to be solved because instead of coming from a technology-centric point of view, which was the way we had approached things in this practice now for eight years at KPCB. I then wanted to take the point of view of looking at needs and markets, and working backwards to what technologies we needed to assemble to solve those problems.

Kiley: How did you go about—well, first, tell me, if you recall, what the books were that you took with you on the sabbatical that led to your epiphany.

Byers: You know, I'll see if I can find them in the home library. Maybe I've still got them there. One of them was the basic biochemistry text of Lubert Stryer. I remember that, because I got the opportunity to meet him along the way, then. About this time, I had become a volunteer at UCSF. I had had some eye problems, and eye surgeries. As I started volunteering there, I had the opportunity to spend more time there, walking the hallways, being introduced to scientists, and so on. I built up a long list of friends who were scientists and doctors in various disciplines, and this helped me enormously, because I got out of my office, and started getting into my habit, which I still have today, of every chance I get, going to a medical center and spending time with the researchers and the clinical researchers, and the practicing clinicians, and other people there, to get closer to the medical need, so that I can be a bridge between them and the business world.

Kiley: What was the nature of your volunteer activities at UCSF?

Byers: Well, because of my eye problems, I first got involved with the vision research center there. There was a foundation called That Man May See, and our goal was to build a new vision research center there. I became a board member and chairman of that foundation.

Kiley: Was that goal achieved?

Byers: It was. We ended up raising about forty million dollars from various foundations including the Koret Foundation and Arnold Beckman, and built a large vision research center and clinical facility there. I then went on to become a board member of the UCSF Foundation, which is the overarching foundation for this world-class medical center and medical school and research facility. Ironically, this is the medical center and research facility that Herb Boyer was at when he made his seminal discoveries and where he was when he founded Genentech. I found out how broad and deep all the science is there and how willing scientists were to share all their ideas and their vision and their creativity with someone who would listen. There were a lot of people there who mentored me then in science. I can point to many of them and I think what served me so well is how many there were. It was the diversity of the ideas that I found was important.

At this time, also, in the mid-eighties by now, it had been eight years since Genentech had been formed, and there were growing up consulting organizations that were now making it their business to describe and elucidate the biotechnology industry. There were more newsletters and more reports, and we had become more sophisticated and aware of looking at industry trends, and prescribing patterns of pharmaceuticals, and incidence of disease, and so on. I took all that information, and as I say, spent most of 1985 studying it all, trying to lay out what would be fertile areas for us to start companies in.

Kiley: Could we go back for a moment and see how many of the people in the medical centers mentored you and enhanced your understanding of scientific needs? Do you recall names? You mentioned Stryer and his book.

Byers: Paul Berg at Stanford, Stan Falkow at Stanford, Don Kennedy at Stanford; at UCSF in ophthalmology, Steve Kramer and Alex Irvine. In molecular biology, Mike Bishop.

Kiley: The latter a Nobel laureate?

Byers: Yes. And of course, all along this time, I was spending a lot of time with, and learning a lot from the people who were working in the companies we were involved with. I want to emphasize that, because it's what we refer to as the network or the *keiretsu*, but simply what it is, is developing over time friendly and sharing relationships with the talented people we hire into these companies. They are in fact, the experts. I would always spend as much time as I could in the labs of the companies that we were involved in, learning as much as I could

about what they did. Now, we've always had a principle at Kleiner Perkins of never investing in a new company that would compete in any way with a company we're involved in. That has served us well, because the management employees of the companies that we were already involved in, or were involved in before, trust that if they talk with us and educate us and share with us, it's not going to harm them or be competitive with them in any way. I think we've always had a great luxury of being not just a one-time event of hiring an employee or an officer or a researcher or an executive in our companies, but it's always long-term relationships. It's kind of the cumulative effect of all that too.

Kiley: Could you share with the reader the etymology of the term *keiretsu*, as it's used here at Kleiner Perkins?

Byers: I'm sure that we have taken great license to the literal translation of this Japanese word and what it meant, just to try to describe what we do. We had this idea that one of the roles we play as an active board member in our companies is to reach out and broaden the network of people that our companies can deal with and get to know, and develop relationships with and common interests. So, we call that a network. Then, I think, sometime, in the early eighties, we decided to put a catchy name on it, and we called it the *zaibatsu*—the KPCB *zaibatsu*. We, in fact, starting in 1980, got the management of our companies together around conferences and so on, like that. We held our first CEO conference in December of 1980. We've continued to do that ever since, to the point now where today, we have quarterly meetings of all of the VP of sales of all of our companies, and then the quarterly meetings of VP-R&D, and VP of Finance, and CEO meetings once a year, and things like that. Sometime, I can't remember, ten years or so ago, someone politely described to us the fact that *zaibatsu* may not be the word we want to use, because it had some negative connotations going back into history of Japan, so we changed to the name to *keiretsu*, which I think has a different meaning, so that's the term we use today.

Kiley: I think the difference is that Douglas MacArthur, when he was running occupied Japan, banned the *zaibatsu*, and the Japanese obligingly reconstructed the network under another name, *keiretsu*. And evidently the network, under whatever name, has been a benefit not only to Kleiner Perkins, but also to its portfolio of companies. Is that correct?

Byers: Well, yes, and that's the point. We benefit only when our companies succeed. The way we look on ourselves, is not so much as financiers or business people, but as service providers. When we meet great entrepreneurs and invest in them, as happened with Genentech and Hybritech, most of what we do is to provide services to them to support the entrepreneurs. It's their success that is fundamental, and then trickles down to us.

Kiley: Has this sort of networking led to active cooperation amongst the companies over and above knowledge sharing?

Byers: Well, it has. Of course, it's all on a voluntary basis between the companies. We just make the introductions and hope that they get along. An example is the first company that I started after my 1985 Europe study was Athena Neurosciences, a company that we incubated in our Palo Alto office. We met a brilliant scientist, Larry Fritz, who we felt would make a good founding scientist of this company to work in neuroscience and go after some of the intractable diseases of that, being Alzheimer's and drug delivery across the blood-brain barrier to the brain, and so on. We then needed to find a president. Well, the good relationship between companies we'd had, and Genentech, for example, resulted in the candidate we ended up hiring at Athena was one of the candidates Genentech was looking at potentially hiring. They hired another candidate, Kirk Raab from Abbott, the company president and COO, when he joined. Someone else who they had talked with during that process was John Groom, who was president of Smith Kline International, and was living in England at the time. Bob Swanson gave me that resume and I talked with John Groom; and he ended up joining Athena.

Kiley: So, neuroscience was one of the medical specialties in which you proposed to concentrate energy after your year of studying. Were there others?

Byers: Yes. I had decided to go after a list of things. One was neuroscience, and what we call CNS diseases, of the central nervous system. Another was cardiovascular. Obviously that's the number one killer of people in the U.S. for sure, and it looked like there were a lot of opportunities at that time so in 1986 we were involved in the start-up of Gensia Pharmaceuticals in San Diego. Another area of interest was ophthalmology and eye disease. Of course, I had a personal experience with that. But one of the things that I realized through my experience with those therapies is that eye drops are something that are dosed very frequently because the latency time of the drugs in the eye was short, so a drug delivery technology looked attractive. That led to our involvement with InSite Vision in '86. Another area of interest was cancer. With very few drugs being efficacious in that field and [those] very toxic, and my exposure to monoclonal antibodies from the Hybritech experience led me to want to found a company to work in monoclonal antibody therapy for cancer. We got involved with IDEC Pharmaceuticals, incubating that company from scratch in 1986. So, that was enough to do in one year.

Kiley: [laughing] I would say so.

Byers: For a venture capitalist, sort of the known average of the number of new ventures one wants to take on in any one year is two, and not at the same time, either. In 1986, with my now specialty in life sciences, I got involved in five start-ups.

Kiley: So they would be Athena, Gensia, InSite Vision, IDEC, and the fifth?

Byers: Yes—Athena, Gensia, In Site, IDEC—hmm. Oh, soon after that, Biosurface Technology.

Kiley: All right. And Biosurface Technology was formed to do what?

Byers: Tissue transplants. It was a new technique to be able to culture and scale-up the growth of human tissue for treatment of things like severe burns.

Kiley: So these five areas that resulted from your year of study obviously reflected your view that they addressed unmet needs. Were there other things in common with those five areas?

Byers: I think of them as vertical applications or areas of need. What would cut across horizontally would be the biotechnologies that had developed over the prior ten years then. So then, we would take cell biology, molecular biology techniques, use of monoclonal antibodies as reagents or perhaps therapies. By then, recombinant DNA technology was not seen as just a way of making proteins as therapeutics. It was seen as a common laboratory technique. All of this had exploded in the prior ten years and to me, felt, it was time now to, as I say, take it and apply all of these technologies as platforms in going after specific vertical markets.

Kiley: Well, certainly when you talk about CNS and cardiovascular and cancer, in particular, you're dealing with refractory diseases. Am I right that it's the refractory diseases, the intractable problems, that get left for the start-ups because the easy opportunities have been taken by the larger, long established companies?

Byers: Well, it's hard to tell. You know, small companies are very open with what they are working on, because they have to attract outside capital. So, they explain in meetings and investor conferences and IPO documents what they are doing. Large companies are not so open, and not having ever worked in one, it's hard to know, but I think yes, there is a risk to going into these areas. When one is thinking of starting a small company, it doesn't make any sense to go where the herd already is, especially large companies, where they have large market share, or where they have a drug that's working pretty well. I think one of the major risk factors for small companies is we tend to go take on really difficult problems. Now the hope of the payback on that is, even though we might fail doing it, if we're successful, we will be the first to do it, and being first is important.

Kiley: I would suggest there is another category of opportunity that falls to the lot of entrepreneurs. I'd be interested in knowing what you think of the following proposition. Sometimes, academic science offers new opportunities replete with low hanging fruit, and then the race is to the quick. Entrepreneurs can be quicker than organizations that have existing businesses to manage, that have stratified

decision making, that can't offer the same equity incentives that entrepreneurs may offer and so on. You witnessed at Genentech a human insulin project that the company completed with twelve employees.

Byers: Yeah, and you would think with the Cohen-Boyer discovery that the company most likely and in the best position to capitalize on that science when it was announced in 1975, would have been Lilly, who was the market share leader in selling insulin derived from animal sources.

Kiley: You mentioned that Hybritech succeeded in producing the first viable monoclonal antibody diagnostic prospect in as little as three months, when Abbott and Roche perhaps between them dominated the diagnostics field. That's another example. Can you think of others?

Byers: Well, I have a generalized theory on this, which touches to your point, which is that I think the opportunity for entrepreneurs is there if there is a radical breakthrough, where there is a paradigm shift, where there is the chance to do something an order of magnitude different, using some breakthrough technology. Why is an entrepreneurial organization more likely to do that? Well, I think it's the nature of large, established companies, that the first objective of that company is to maintain market share. Much of the R & D spend of large companies is allocated to what we would call sustainable engineering, or sustainable science. It's all science and improvement and endeavor to improve the existing products and to sustain them, because it's better to protect and reduce the cost of manufacture of existing products, and that's a rational thing to do. The amount of money a large company, in 1978 would have put into monoclonal antibody development would have been paltry, probably on the size of what we spent at Hybritech. What we learned in life sciences in the biotech industry, in the eighties, was that if we focused on one area, and put all of our wood behind that arrowhead, and put substantially more venture capital into it than we used to do in the early days in the seventies, we would spend more on that project than a large pharmaceutical company would because they have fully allocated budgets every year, and to start a new project at a big pharmaceutical company, or a big diagnostics company, is a tortuous process. Some intrapreneur there has to convince management that it's a good idea, and get some budget allocation and get some resources, and a team, and a lab, and so on like that. What we're starting to know though, is it's easier to move faster.

Kiley: All right, now, let's compare entrepreneurial teams in small companies to academic scientists in prestigious institutions. It's right, isn't it, that for at least the early and perhaps, the mid-stage of biotechnology's evolution, the distance between the lab bench and the success that could attract capital and perhaps riches was not great? How were small companies advantaged, if at all, in competing with such as Harvard, Stanford, MIT, and so on?

Byers: When—in hiring scientists?

Kiley: In achieving scientific breakthroughs, in competitions to clone important proteins, to hatch new platform technologies, and so on.

Byers: Well, I'm not sure I know. I think I look at it differently. I think that up until biotechnology companies were formed and the industry began, all science research in the biological area took place in academic centers or research institutes, or something like that. I think when the biotechnology industry developed and developed rapidly over those ten years we just covered, it became, over time, acceptable and okay for brilliant scientists to go do their research in industry.

One of the things Genentech did so well, was it created a culture of research where scientists could go there, and know they could publish, know they could have seminars with their colleagues in academic medicine. Genentech, I think, did such a service to the biotechnology industry by being the first successful company. It set a standard, and the standard it set was that research should be done, in industry, very much like it was done in academic medicine—with a sense of freedom.

And so it was, in a way, this healthy competition between biotechnology research done in academics, or done in industry, that that line was not a bright line. Both could publish, scientists in both areas could get visibility and be proud of their work. I think each venue made the other better. Over time, I think that's what we've seen. There's a fluidity of scientists just moving from academics into industry and back.

A good example is Rusty Williams, who was at UCSF and had a large lab there and was a discoverer of PDGF and IIB and IIIA, and these other important discoveries; then started Cor Therapeutics, spent some sabbatical time there; stayed at UCSF; went to Chiron for five years as chief technical officer; and recently this year, left to start his second biotechnology company called 5 Prime Therapeutics. This is the new scientist phenotype.

[End Tape 2, Side A] ##

[End of session.]

Interview 2: October, 2, 2003

[Begin Tape 3, Side A] ##

Kiley: It's about 12:45 p.m. This is Tape 3, Side A, of the second interview of Brook Byers. It's being taken at the Menlo Park headquarters of Kleiner Perkins Caufield & Byers.

Brook, in our last session, we talked about relationships and biotechnology companies and academic centers. I'd like now to talk about the relationships between biotechnology companies and Big Pharma, and how that has evolved over time in your view. Perhaps a good way to begin would be to ask precisely what is a biotechnology company, and has the nature of biotechnology companies changed over time?

Byers: Well, it has changed over time. On this topic, and many of the other topics we're going to talk about, it's hard to generalize across all companies because today there are probably 2,000+ biotechnology companies, and all of them have different degrees of independence or dependence on sources of capital and technology, and they have different product strategies, and so on. But I think "biotechnology company" has changed. Early on, about twenty years ago, in the late seventies, early eighties, it meant the company whose founding scientific platform was around biotechnology techniques and science. And so, that would be recombinant DNA, molecular biology, monoclonal antibodies—these things—and that was all new. Today, I think "biotechnology company" is part of the lexicon just to describe a company that uses those techniques, and might also, and probably has, product programs that came out of that—so it has drug lead candidates or candidates in the clinic or diagnostics that come out of that. Ironically, in a way, since all large pharmaceutical companies have now adopted biotechnology in their R&D programs, you might call them a biotech company. So today, what a lot of us do is, instead of talking about a company as a biotech company, we talk about it as a biopharmaceutical company. That's a hybrid word we use to say, it's a small pharmaceutical company, or new one—tiny in comparison to Pfizer and GSK, but that the founding bases for it were the new science.

Kiley: GSK is GlaxoSmithKline?

Byers: Yes.

Kiley: Would it be fair to say that a biotechnology company is a development stage company trying to become a pharmaceutical company?

Byers: Yes. The term biopharmaceutical now—I think the reason we use the hybrid is we want to make sure that the understanding is that companies that we do, are not based just on science now. They are working toward products.

Kiley: When Genentech began, Bob Swanson expressed the ambition that he wanted to build a major independent pharmaceutical company. He certainly succeeded, with the help of his successors, in making a substantial company, albeit one that has lost a measure of independence. Given the sparse number of companies that have become pharmaceutical companies growing from biotechnology roots and retained their independence, what would you say the prospect is presently for a discovery-based company to become a major pharmaceutical company and retain its independence?

Byers: Well, if we look at the statistics, over the past twenty-five years that the “biotech” industry has been operating, there are a couple of dozen companies now that came from this sector and have grown in to be profitable companies that are independent and stand alone, that have products on the market that are curing disease or reducing suffering, large sales supporting the enterprises there. So, it does happen. Now, the funnel of companies that have attempted to become one of those is measured in, as I said, hundreds and thousands. So the pure statistics of it look as though the chances are slim, but it is a marathon, not a sprint. This is an industry where everything takes a long time. Just discovery takes a few years. Then the preclinical work, and then the clinical trials, and then—rightfully—the scrutiny by the FDA [Food and Drug Administration] before something is approved to be widely marketed. It’s a very long time. Everything happens in this industry very, very slowly compared to information technology industries where product development might take two years, but then the product can go on the market immediately and a company could be profitable within three years of founding, maybe four, something like that, on capital of twenty-five, forty, fifty million dollars. Profitability in this industry requires—for a pharmaceutical—eight to ten years, and hundreds of millions of dollars of capital.

There are always pundits who say during the cycles—and there is a cyclicality to the flow of capital to biotech—that during the bad times and the slow times of capital flows—and we saw that in the late eighties, we saw that in the mid-nineties, we saw it again in the early part of this millennium around 2001 and 2002—that companies are going to wither away, run out of capital, close down. There’s going to be huge consolidation. People start hanging the black crepe. This has gone on four cycles now in my career. The remarkable thing is that the combination of the power of the technology and the value of the intellectual property developed by it, the never-say-die entrepreneurs and their remarkable resiliency and their ability to scratch out financing from somewhere, is that we still have so many biotech companies moving forward, each with their own strategy, each with their own plan. So, I think we’re just going to continue to see

this very slow process. Yes, some of it has got to be Darwinian, but it's remarkable how few failures there have been.

Kiley: You mentioned in our last interview that Hybritech sold itself to Eli Lilly because it needed more capital than it could otherwise raise in order to exploit all the opportunity that it had created. I have been told that Genentech sold a controlling interest in itself to Roche for that same reason. Is that the most likely outcome in the future for drug-discovery-based biotechnology companies?

Byers: I think it is, probably, for many of them because just the sheer reality of the amount of capital required is such that, taken together with what appears to be the cyclical or the fickleness temporally of the public capital markets won't always line up right for companies. There probably is not enough capital for all of them that's willing to be risk capital *and* for biopharmaceuticals. Also, the willingness of the large pharmaceutical companies to be capital provider and in many years—the slow years when the public markets and venture capital are not providing that much capital—the pharmaceutical companies are providing the bulk of it, measured in billions of dollars, into the biotech industry. So, yeah, I think over time, that lack of independence will occur.

Now, independence is a complex word here because large pharmaceutical companies don't necessarily want to own or control the small companies. They realize that the creativity of the small companies is just what they want to tap into. So what they do is they attain control in other ways. They attain control by partnering on a product program, providing full-time equivalent funding of two hundred, two hundred fifty thousand dollars a year, and payment of milestones to the small company, and sharing of costs of clinical development, and so on like that. But of course in return for that, the large pharma company wants marketing rights. That's another form of control. It's controlling a product, not the company. Small biotech companies, and growing medium-sized ones have used this as a financing technique for the past twenty-five years. The consequence of that is that a lot of control of the products or the future upside of the small companies has been given over to the large pharmaceutical companies. That's almost a unique characteristic of this industry versus other technology industries that I'm familiar with. It has to do with this huge need for capital, which has to do with length of time of product development.

Kiley: Has the appetite of Big Pharma for symbiotic relationships with biotechnology companies changed over time? Have those companies become more cautious? Are they looking for different things now than they did in the earlier stages of biotechnology?

Byers: Actually, I think it's grown. I don't think they've become more cautious. It's a little complex to measure because the hundred top pharmaceutical companies around the world have been merging with each other, so looking at the statistics is hard for me to track. But I think the numbers, in terms of partnering per year,

for the past couple of years has been about five billion dollars of money flowing into biotech industry companies. That's up from ten and fifteen years ago. Twenty years ago, early on, there were just a few pioneering companies. Lilly, in its landmark alliance with Genentech over human insulin was huge. Then Lilly bought Hybritech in 1986. That was a bold move because Hybritech had only a few small diagnostic products on the market and some theories and product programs and development about therapeutic antibodies. Merck was known for not partnering with any biotech companies for a long time: I think until the 1990s. It has broadened now. In fact, there are a lot of pharmaceutical companies that don't get a lot of public attention. These are privately owned ones in Europe or in Asia, or medium-sized ones, we might call them, that are now partnering with small biotech companies too. One is Ares-Serono in Switzerland which has benefited greatly by partnering in a very clever way with small companies. I think the symbiotic relationship will always be there.

Kiley: Have European and Japanese companies grown more weary in view of product failures that they've encountered in earlier licensed products?

Byers: I'd say grown more sophisticated, so I think the nature of the relationships has become more of a true partnership. Early on, it was Small Company would say to Big Company, "Give me dollars. Give me money so we can run product programs, and we'll do a combination of equity and milestones and research support and all of these things, and for that, I'll give you the Japanese market or the European market," or something like that. There have been a lot of product failures. You see them when you get into the clinic in phase I, II and III human trials. We see them of the small companies because those companies, by nature, are more transparent, and tend to announce all their activities. They announce their success in phase I and then when it fails in phase III, well, it has got to be reported on. Large companies don't report their failures so actively, especially earlier in the pipeline. Small companies report the filing of an IND [Investigational New Drug]. No large company reports the filing of an IND. Small companies, especially ones that have gone public well before they are profitable, want to continue to have investor interest, so they announce all these things. I think large companies experience probably similar failure rates—it's just it's not publicly known. That's why I say "more sophisticated." I think there's more sharing. Partnerships today have joint Research and Development committees that are more open in talking about the facts. By nature—whether we call it biotech or biopharmaceutical or large pharmaceuticals—this is a very risky business. The chance of failure of compounds is well documented. I think everybody understands that. That's why people need a full pipeline. That's why I think the creativity of the small companies will always be attractive to the big ones.

Kiley: To a small company these days, in the new millennium, that dares to dream of becoming a pharmaceutical company on the strength of its research and own

clinical development, how many shots on goal is it likely to have, relative to a big company?

Byers: Well, that's a great question. We used to think simplistically, back in the 1980s when we were starting companies like Athena Neurosciences and IDEC and Ligand and Arris and all of these, that we wanted to have at least three programs. We were more sophisticated than this, but to boil it down, we would say: "Three programs, and out of those, over the years, we'll partner one to get a lot of funding to cover overhead; we'll keep one; and one will fail before we get to do one or the other of the first two with that." So we at least had to have three shots on goal and they had to be not mutually dependent. In other words, not have the same biological target or the same molecular entity doing it.

I think it's different today. Today, so many of the clinical targets have been pursued. So much of the technology is much more sophisticated and broad now that today, for a company to begin, it seems as though, companies have fallen in two broad categories. One is either what we call a product-oriented company. That is a company that starts early on with lead compounds or possible drug candidates. Those come out of academia or by putting a couple of small companies together that don't have critical mass. There's a funding interest in product companies—has been for a few years now. For a science-based platform company, those were out of favor for the past couple of years. I see them now in 2003 coming back in favor so long as they have a product story connected with it that comes out of that platform. And that is reminiscent of ten years ago to me. I think in the ebb and flow of this industry, we are almost *déjà vu* all over again now. That's what Ligand was. Ligand was a technology platform built around intracellular receptor targets, a new concept in the early nineties, and then was developing and had some ideas for products early on. For that whole set of receptors, there were literally a dozen good targets. So today, in the post-genomics era, companies are now expected to apply the output of the Human Genome Project, but that's not enough. That's just another tool in the armamentarium to develop drugs.

Kiley: It seems nowadays that it's difficult to attract the attention of a Big Pharma collaborator unless you've got human clinical data. Certainly, that is different than my experience in the earliest days of biotechnology, and it significantly raises the bar for companies seeking partnership. Would you agree?

Byers: It is. It is frustrating to the small company, because to get to human data—let's say, phase IIA data—the venture needs to have raised tens of millions of dollars to get to that point. If they can't get it from Big Pharma, who have tens of billions of dollars of cash to do these kinds of things, then they have to get it from venture capital, late-stage private equity, early-stage IPO. Early stage IPO has been inactive for a couple of years, so this is a quandary. I think I understand the motivation for the most part of large pharmaceutical companies because over the past five to eight years, they have done a lot of collaborations that have given

them plenty of targets for their R&D operations. So what I hear from Big Pharma is, “Hey, we’re target rich. We need to focus *our* activities. We don’t need any more targets. What we need more of is things that are more mature.” Bear in mind, you have to understand, in a large pharmaceutical company, every year the R&D budget is fully allocated. There are people in that company who are intrapreneurial, just like the entrepreneurs in small companies, and they all have their favorite projects and their absolute fervent belief that their programs are as good or better than the ones out in the small companies they read about in *BioWorld* every day. They’re fighting for the money. The biotech companies are going to Big Pharma asking for funding, and it’s a tough job for the heads of R&D and business development of large pharma to decide: should they spend it inside or outside? Now, over the years, the proportions spent on outside has increased. In fact, some large pharma companies say that’s the trend. They’re going to spend more outside. Well, why? There is a belief, and I subscribe to this, that there is an efficiency of creativity and innovation in small companies. It’s also, if a large company is going to spend more money outside, easier for them to then cut legacy programs that they probably didn’t have the guts to cut before. It can be, in a way, a forcing function to cut programs. That’s another way of saying “downsizing their own internal R&D,” and cost-cutting is going on in large pharma, even after the mega-mergers. Finally, I think it’s worked out. There are products that have come out of these collaborations that have been big successes for everybody.

You know, the thing to keep in mind about this industry once again is, “where is the risk”? What’s different about the biotech industry and the pharmaceutical industry—they have this so much in common—is that there is a high technical risk of the product being developed to work, but very little market risk if it’s an innovative product. In other technology industries—software, telecommunications, computers, and so on—there is relatively little technical risk. There’s the risk of developing a product, but usually, the risk is on schedule and cost of development, but there is a high market risk. Will enterprises accept this new computer routing technique? Does the world need faster CPUs? Does the Fortune 500 business community want to reorganize their databases, so they can have a view across all divisions, and so on? Then, the ease of entry to developing those products is much less because there is less technical risk, and so all that market risk is there. I’m always struck in my firm, Kleiner Perkins Caufield & Byers, listening to my fellow partners every Monday in the Monday partners’ meeting talking about their software company or their telecom companies, especially in the past two years, where good technology was developed but the markets evaporated. We have some telecom companies that developed optical telecom components, or systems to make fiber optics more efficient, and there were no orders in some months. None! Whereas, in medical devices or a new drug, or a new diagnostic, if it works, there is a 1.8 trillion dollar US industry there, year in, year out, ready to buy. Admittedly, there are problems of reimbursement and pricing and issues like that, but if someone can make a breakthrough in human health care, there will be a market.

Kiley: Would you say that's true even if it proved the case that government and other reimbursers refused to spend a greater percentage of GDP [gross domestic product] on healthcare than is presently spent?

Byers: No, I think that will stifle innovation, and it'll be a cascading effect with unintended consequences I don't think we can foresee.

Kiley: We are spending 14 percent, give or take, of GDP on healthcare now. How much more can we spend? Or is it a question of squeezing the water out of present inefficient or ineffective practices with new and better products?

Byers: I've seen the statistics and 14 percent looks high compared to some other countries, and sounds high because that's a lot of money. So I have a couple of reactions to it. First of all, the drug component of that, I believe is around 9 percent. I am of the philosophy and the belief that drugs are the most efficient way to treat disease, as opposed to later intervention when the disease is out of control. That's often surgery, long-term care, hospitalization—all of that—much of which is not curative. It's just a stopgap kind of thing.

Kiley: Some would say the best way to treat disease is to prevent it. Preventative medicine as against curative medicine. Have you ever looked at investment in companies whose hallmark was preventive medicine? An example would be a vaccines company.

Byers: We have, and I was going to come to that example. The best bargain in healthcare is a vaccine because it's protective for ten years, and the prices are relatively low. We almost didn't have vaccines until Smith Klein Beecham, before it merged with Glaxo, and Chiron, and some others had the courage to step up and develop recombinant vaccines, which were safer, and I think helped them to have the courage to go ahead and do that, even though the liability question was still out there. This is before Congress rationalized the liability questions on vaccines. You know, it's back to risk. There are people in society who think things should be riskless. Everything has risk. There is a risk of getting the disease, but the risk of the vaccine is much less than getting the disease. Back to the economics—the dialogue I don't hear much about is 14 percent spent on healthcare—I know the services side of that is wasteful, and the administrative side is wasteful. But whatever the percent is, if it's 10, 12, 14, 15—what's more important to spend money on? This is all about life and the quality of life.

Kiley: Has Kleiner Perkins invested aggressively in healthcare services? Bioinformatics, data management, others of these areas in which you say waste resides?

Byers: We have done that. We've done a few of those. The most notable one is an incubation that I started in the mid-nineties, right after we had an early success

with Netscape. I incubated a company here in the offices called Healtheon. The goal was to take the internet, which was a new powerful technique of moving data and linking and browsing, even in business, and going after the whole issue of how information flows in the healthcare industry. In studying it all during the incubation period, we decided to go after charge capture—how charges were accounted for, and how payment was made from payers, and try to add efficiency into that system. Because that's all part of that administrative three hundred billion dollar a year piece of the 1.8 trillion dollar healthcare economy. That company has gone on to be a big success because of its initial founding, and the ideas it had, it became attractive to some other pieces—WebMD, which had content; Envoy, which had payment systems—so through a series of mergers and acquisitions, Healtheon/WebMD today is a large company, improving on that. There are other software companies and physicians practice management systems for individual doctors. Prescription capture and charge capture right at the doctor on a personal device like a Palm Pilot or an iPAQ from Compaq.

[End of Tape 3 Side A] ##
 [Begin Tape 3 Side B]

Kiley: This is Tape 3, Side B, of the Brook Byers interview.

You mentioned bioinformatics, which is another one of these hybrid words of biotechnology and informatics. What it's really about is applying computational techniques from the computer industry—and software and transmission of data and databases inquiry—with biology and all the things that go into drug discovery.

Byers: This is something that's received a lot of attention in the past ten years. It has become a key part of drug discovery and has improved the efficiency of it greatly. There's always been the use of computers in labs, for setting up experiments and capturing data and project management timelines and so on. Where bioinformatics really rocketed was with genomic data because the databases were so huge. Any sequencing operation in the Human Genome Project or people running an Applied Biosystems 3750 in their discovery labs generates terabytes of data. Storage became a problem. How would that be stored? In what formats, in what database formats? Oracle and SQL and Sybase were not sufficient because these were new kinds of data and so much of it. Then how do you inquiry it? These aren't words. New software needed to be written. And then, how all that genomic data then is tied to hands-on molecular biologists who are suspicious of all this kind of stuff that comes from computers because molecular biologists, biochemists, cell biologists, they work with the real stuff—the wet labs. There became this new vernacular—there's wet-lab biology and then there's *in silico* biology, which is talking about all the stuff that comes out of bioinformatics.

Interestingly, most of the bioinformatic software came out of academia. There is a department at Stanford University just a few miles from here that offers everything it develops on the Web for free. I mention that because a lot of people ask me, why isn't there a bioinformatics industry? There are some companies that have started and are still around that offer bioinformatics software for a price. It's not a large industry because so much of the software is either offered for free from the academic developers, or the larger customers—the large pharmaceutical companies—develop their own. So there has not developed an independent merchant software industry in pharmaceuticals and biotechs as there has been in other industries. If we look at the utilities industry or transportation or even the software industry itself, financial services, you know, if you go to American Express, Schwab, Merrill Lynch, Morgan Stanley, Bank of America, airlines—American Airlines, United [Airlines], and so on—there are huge data centers. There are enormous software operations, and they buy much of their software from outside vendors. That's how we have huge companies like Oracle and SAP and BEA, and that's why so many of my partners focus on software startups. It hasn't happened in bioinformatics. I think a lot of it has to do with the hyperconservative proprietary nature of drug discovery. Every company doing drug discovery wants to be very protective of their compound libraries and their molecular structures and what projects they are working on. There is not a sharing. For there to be a merchant software industry, there has to be a set of customers who will all buy the same standard product, and that really never has happened. I think it goes back to the almost paranoid nature of the pharmaceutical industry that they're not collaborative with each other either. They all stand alone.

Kiley: Certainly my impression in the mid-seventies when Genentech began to interact with large pharmaceutical companies was that they had not been terribly collaborative up until that time. On the other hand, it is fair to say, is it not, that they have shown great virtuosity in collaborating with biotechnology companies in the ensuing decades? I hear *you* to suggest that they do not collaborate one with the other amongst members of the Big Pharma community.

Byers: That's right. I think it's because they fear each other, but they don't fear the small company. All the power in the relationship between a large pharma company and a biotech venture is with the large pharma company. They have the money. They have the marketing power, and they look to the small company as an interesting R&D shop. They might tolerate in the arrangement made, to give co-development rights and then—more recently in the past five, ten years—co-marketing and co-promotion rights. I think actually, those were often given to the small company as somewhat of a gesture of the large one, thinking, "Well, they'll never come to pass because this little company will never have enough money to mount a marketing operation." Sometimes it's turned out that the small company, because of the success of the collaborative project, was able to catch an open window in public financing, raise hundreds of millions of dollars, and in fact, launch a marketing operation.

An interesting example of this is the Genentech-IDEK relationship. I want to talk about that one because we have now biotech companies of the first generation that have become the funders of the younger ones. Genentech is very collaborative now, as the holder of the money looking to collaborate with small companies and must have dozens of these relationships now, in the past five years that look much like the ones that Amgen, Genentech, Hybritech, Ligand, had all struck with big pharma in the eighties, early nineties.

Kiley: You were involved in the formation of IDEC Pharmaceuticals?

Byers: I was.

Kiley: Will you describe the nature of the IDEC-Genentech relationship?

Byers: Yes. It's instructive to have a little history on IDEC. IDEC was started in the late eighties to work on anti-idiotype antibodies. Along the way, that was proven to be too difficult in the clinic and too difficult in manufacture at a low enough cost to make it a business. The team at IDEC on the scientific side—Nabil Hanna and others and the CEO, Bill Rastetter came up with an idea to pursue a specific antibody that they thought would be useful against B-cell lymphoma. That's an antibody against CD20 epitope, so the anti-CD20 antibody. That product is called Rituxan now. IDEC in the early nineties was a small company in need of money, and in the early nineties, the public markets were not forthcoming with that. I was chairman of the board at the time, and I remember we went out to do a PIPE financing. We were already public, and a PIPE is an acronym for Private Investment in Public Equity.

So it's a private placement by a few investors in an already public company, and we were able to raise a grand total of six million dollars. Now, contrast that when you're in a good period like today—PIPEs are raising sixty to eighty million dollars. IPO's are usually in that range. A PIPE is a follow-on public financing and sixty to eighty million, a hundred to a hundred twenty million is not unusual. In the summer of 2003, there have been plenty of these.

But such was the case in the early nineties for IDEC. So, having only been able to raise that much, it was clear to us that we needed a partner. We went to a large pharmaceutical company on the East Coast and showed them our data. They talked with us for months and it wasn't going very well. They were very skeptical a young company could have something this good, and could we manufacture the pilot amounts and so on like that—very difficult conversations. So we went up to Genentech, which we felt at the time could use another product in its pipeline, and they liked it. They provided program funding to complete the R&D, funding for the clinical trials. They believed in the clinical trials that IDEC were running because the IDEC clinical development team were very good under Antonio Grillo-Lopez, who had been hired from a large pharmaceutical company. Genentech granted to IDEC future co-marketing and

co-promotion rights. Because of the success of the product in clinical trials and its efficacy, IDEC was able to raise significant amounts of money when the funding window opened later in the nineties—’96, ’97 period. It raised a couple hundred million dollars on the public markets. It raised debt financing. It got some other financing from a Japanese partner. IDEC was able to fully integrate, build a manufacturing facility, build a sales force, and go out and market Rituxan. Through this collaboration between the two, it’s been a marvelous outcome because Rituxan today is a billion-dollar drug. It sold a billion dollars worth of product last year.

Kiley: Are you in a position to identify the East Coast pharmaceutical company that said no to this billion-dollar opportunity?

Byers: I am, but I’d rather not. I think there are people there who are kicking themselves and they know who they are.

Kiley: You’ve referred several times to the cyclical nature of capital markets for biotechnology. To what do you attribute that cyclical?

Byers: Well, I see the cyclical nature in the capital markets for all technology. I attribute it—oh, it’s a good question—to a combination of factors. One is our whole economy is cyclical. We didn’t want to believe that a few years ago when books like *The Long Boom* came out, and all of this. But, in fact, there’s some to that. Layer on top of that the fact that this is a very risky business, so there is speculation in investing in these companies. It’s higher risk, higher return. There are periods of psychology where taking those risks is tolerated, and there are periods of time when investors—private and public—are of the psychology they don’t want to take that risk. That’s an amplifying effect. Another round of cyclical has to do with how is the biotechnology industry doing? There are plenty of publications that study all this and produce reports weekly, if not daily, about how products from companies that are in clinical trials are doing. If there is a period of time in a couple of months where there seem to be unrelated, but a series of failures in the clinic, then the psychology turns worse and there’s even more amplification. Or, in the reverse, if there is a series of FDA approvals and great outcomes in the clinic, it goes the other way. We’re in a period of the latter right now, because Genentech’s pulled a hat trick and gotten three drugs approved by the FDA this year. There’s a euphoria because of that, and some of those were drugs that came out of collaborations with small biotech companies.

Kiley: Is there a risk stemming from that euphoria that the window will open so wide that bad companies as well as good will get financed and later disappoint?

Byers: Yes. The great thing about a free enterprise system is anyone can start a company. Anyone can build a company. One of the problems with a free enterprise system is it’s a free-running system and excesses happen. Great amounts of wealth are created, and great amounts of wealth can be lost. But

that's a free market system. We always seem to have these excesses. Should the window have shut so tightly on public funding of biotech companies over the past couple years? No. There are plenty of fine companies moving products through that really should have received more attention, but they didn't. Now, we're going to come into now my fifth—if we call them bull markets, or open windows for biotech public funding—and it's going to happen. Every time we say, "Let's have the investment bankers have a tight filter on quality. Gosh, a lot of the people managing the portfolios—Fidelity [Investments] and Wellington [Management]—and all these people, these funds that buy these IPOs—they're going to remember the past and they're going to have a tight filter on quality," and so on. But, for each company, look at it from their point of view. The goal of the company is to raise the money and manage their business. The greatest fear of a CEO is running out of money. When a CEO has a chance to raise money, they're going to raise money.

Kiley: Are you suggesting that when an investment banker has a chance to earn a commission, he's going to take it without necessary reference to the long-term endurance of his client?

Byers: Well, these things are hard to figure. When there was public funding provided to IDEC before its product came on the market, someone had to run the spreadsheets and say, "Well, how do I think this product will do?" For an investment banker and their analysts and people who buy the IPOs or buy the follow-ons—I have a lot of respect and sympathy for how hard these decisions are, because they're trying to make a scientific decision, a clinical/medical decision, a business model decision. How will it be priced and reimbursed? What will be the adoption rate by skeptical doctors who don't like change, but desperately need a breakthrough? All this woven together. It's one of the frustrating but thrilling things about this industry. This has got to be the most complex industry in business, by far.

Kiley: Multifarious is the word that often comes to my mind.

Byers: Yes, I was thinking of that word. [laughs]

Kiley: I know you were. Let's talk for a while about Kleiner Perkins Caufield & Byers. The first Kleiner Perkins fund was eight million dollars. In our last interview you said the first Kleiner Perkins Caufield Byers fund was fifteen million dollars. What, if it is publicly known, is the largest fund KPCB has raised?

Byers: I think it was the last one, the one we raised in early 2000. That was our [KPCB] X fund. That was around six hundred million dollars.

Kiley: So while the fund was growing, shall I say, 36-fold from KPCB I, what was the fold increase in the number of partners and principals at Kleiner Perkins Caufield & Byers?

Byers: We went from four to ten.

Kiley: Three-fold increase in partners and 36-fold increase in funds. I presume that the number of years over which your limiteds expect to get liquid in a particular fund hasn't changed significantly.

Byers: No, that's the same.

Kiley: All right. So that means now you have to push an elephant through a keyhole without a substantial increase in staff. My question is, what changes in your approach to investment, given the Brobdignagian nature of that elephantine task?

Byers: I think probably the best comparable of a fund today to one in the past is not so much a fifteen million dollar fund—that lasted us about a year and a half, something like that—but more the kind that we raised in 1980, which was a fifty-five million dollar fund, and four partners. So, if you do the quick math, you can see that's about thirteen million dollars a partner. Today, when we raise a fund, the kind of general modeling we do is about fifty million dollars per partner. Back when we raised the 1980 fund, we thought, "Well, it will have an active new investment life. It would be putting new company start ups and so on into the fund for about three years." That's kind of our model today. That model has actually been remarkably stable. It's just that we put a lot more money into each company. Why? One, is that it just takes a lot more money to build a company today. That was a very long time ago—twenty years.

Kiley: Is it simply inflation? Or are there other factors at work?

Byers: That's an excellent question. A lot of it is inflation. Most of the start-ups we do are in technocentric geographical areas, and they have a high cost of living. The level of people we like to hire, we think, improves over time, and they are more expensive. All of that translates to salaries, which is a big component of a technology-based company. It's usually at least half. In software companies, it's 80 percent. In biotech, you buy a lot of beakers and chemicals, though. So that's a lot of it. Another fact that has to do with it is time is the enemy to a small company. Over time, as there is more understanding of technology, large companies use technology within themselves. Small companies too—there are more start-ups today than there used to be. There are more venture capitalist funding start-ups today than there used to be. Remember, you don't need a license to do any of this stuff in the United States. There's the competitive factor and that translates into speed.

One of the risks in small business is being left behind. This is a tension in a start-up always, is how much to spend responsibly in developing a product, as we reduce risk over time by those expenditures, versus going fast. Now, we saw the extreme bad of this during the internet bubble, where the term, "get big fast" was

coined, and actually became a rallying cry of strategic planning of Internet companies, and was used as a justification that because technical risk was relatively low to start a business-to-consumer software—an internet company, or some other kind of internet services company, or something like that, and because they were consumer-facing or enterprise-facing, there were going to be a lot of competitors, and so many companies would be starting, it was important to get to scale fast. “Get big fast.” Well, how do you do that? You spend a lot of money fast, early on.

Kiley: Amazon.com.

Byers: Yes, they did that. There’s one where it’s worked out. Amazon has turned into a spectacular success, but it was the first in its category. It did spend a lot of money and lose a lot of money. Some people argue it could have gotten where it is now by being more “slow and steady wins the race.” It’s hard to tell looking back because there were a lot of people who started up to compete with Amazon, who have failed. Amazon did capture market share and keep it. I think what we all have learned either by going too fast or too slow is that there is a good judgment rate at which to run a company, and this gets back to the philosophy of start-ups. A lot of the secret sauce of why an entrepreneur would take money from a venture capitalist—as opposed to from some other source that wasn’t going to be as involved—is that the entrepreneur must believe that in return for having an activist board member who they’re going to have to interact with and listen to and so on, that in return, they’re going to get the judgment and the collective wisdom learned from all that firm’s successes and mistakes about what is the rate at which you should be spending money in a start-up—a hundred, two hundred, three hundred thousand dollars a month—and how are you spending that money to reduce the risk, and staging the financings at each risk-reduction tipping point. This is the essence of venture capital stage funding and building a start-up correctly.

Kiley: Would it be fair to say that in the latter years of your career as against the earlier years, you have been making bigger bets on a per company basis?

Byers: Yes.

Kiley: I have heard it said by others at Kleiner Perkins that one of the things that attracts you to a potential investment is the opportunity to start a new industry. Now, let’s talk about biotechnology. Is there an opportunity to start a new industry from within biotechnology? Has that been done? Then we’ll go on to talk about what new industries might come from biotechnology in the future.

Byers: Well, there are a lot of things in that question and they have to do with the art of the possible. They also have to do with the motivations of people in venture capital in our firm, and myself, for example. I’ve been doing venture capital for thirty years. I’m not motivated to do the fifth or sixth company in a product area,

or a technology area. No. I think that's not good use of my experiences, and it's not intellectually interesting to me. I think that's true for most of my partners here. They operate in a firm with a thirty-year legacy and a lot of success. We have backed almost 400 start-ups. We've had over 200 IPOs out of those 400. Many others have been acquired. So we're not out there trying to establish a platform or a base. We know that we can provide a good rate of return to our investors—which is our primary job. Intermingled with that is what excites us to come to work every day and be motivated. What really excites us is working with entrepreneurs, especially working with ones that are doing something bold and different. This is how we get to this comment we make about starting and building new industries. What we're trying to say is, "do something bold and different." Within that we're saying that we are not afraid of risk.

Success has paradoxes. One of the paradoxes of success for some people is that they lose the willingness to take risk. They decide that their reputation and their personal financial situation and whatnot are such that it's good enough, and they don't want to risk all that again. For my partner John Doerr to boldly get involved in a new start-up with a product category that has never been heard of before, and take a lot of product development risk, a lot of market risk and team risk and financial risk and all of that, I think that's remarkable, because here's a guy who has a world-renowned reputation of success for what he does, and he's willing to put all of that on the line again. There are many people who won't do that anymore. So, what's the safe thing to do, is to do a fast-follower strategy in venture capital, and there are entrepreneurs who do this too. They decide to be a fast-follower. One of the many problems with that is large companies have become really good fast-followers. In biotech, large pharmaceutical companies have whole groups that have studied biotechnology and studied the biotech industry and go to all the same conferences and they're just watching and waiting. When they think the time is right to apply their huge resources, they will do so. Same for Microsoft. Same for IBM. Part of their strategy is, "Pioneers get arrows. Let's let these crazy venture capitalists and these crazy entrepreneurs out there run around and kind of figure it all out, and once we start to see a pattern forming out of the chaos, then we in the large company will jump in." They can jump in with their own program, or they can jump in and collaborate with the leader, but they don't have to figure it all out for a while.

In biotech, the large pharmas generally sit back. I think that's back to this question you asked earlier about they tend to want to do products that are in clinical trials because, yeah, let those crazy venture capitalists and entrepreneurs run around and beat themselves up, and get all scarred up, and then we'll just come in when it's a little safer. It's this taking risk thing that's so important.

[End Tape 3, Side B] ##

[Begin Tape 4, Side A]

Kiley: Brook Byers interview, second of the series, side A. The date is October 2, 2003. The time is 2 p.m.

In my career in intellectual property law, one of the things that turned me on was that every day I got to deal with the new. That's what kept me coming to the office. Now in your thirty years of venture capital, most of which has been devoted to biotechnology, you must have seen just about everything, so what keeps you coming to the office today? What's new on your horizon?

Byers: Well, it's probably a combination of a couple of things. One is that I am a risk junkie. I find that I feel most alive in my profession and in my work when I'm taking risk. As we were just talking about the ability to take risk and people becoming risk-averse, for people like me, and I'm not unique, they like that. Great entrepreneurs are that way too. They can not only tolerate risk, but motivate off of it. It's a remarkable phenomenon. The other part of it is just the intellectual curiosity. I don't mean "just." I think it's so important about always learning. I would do this job for a dollar a year. I just love it. As we say, it gets me up in the morning. I'm lucky to be paid to learn new things, to be on the cutting edge, that's very exciting.

Kiley: That actually harks back to your reaction at the brown bag lunch when you were at Stanford B-School—when you learned you could get paid to learn new things.

Byers: That's right.

Kiley: And now thirty years later, it's still turns you on.

Byers: It still turns me on. Thirty years in the biotechnology industry, one might ask, so, what's left? That's a long time for an industry. Hasn't it matured? Has it run its course? Most of the investments have been made. There are large companies now doing it—large biotech companies, large pharma companies. Is there any sense of pioneering left in it? The answer, remarkably, is yes. There is a lot left to do. Whereas back in the early days, someone such as myself could follow that process I described in the late eighties of doing a whole study of clinical need and going out and finding technology and starting all these companies, I think biotechnology is much more sophisticated today, much more complex. There's more technology to grasp and get and understand. There are a lot more companies already out there, so the competitive analysis of who's not doing something is more complex. And who's best at doing that? It's the entrepreneurs. We always have to remember that this process of starting new ventures and building them is driven by entrepreneurs, whether they be scientists or business types or whatever. It's not driven by venture capitalists or consultants or lawyers or academics. It's these entrepreneurs, and they're the creative force. Every time I read an article that says, "Well, you know, it's all

been done. There's not a next big thing," or an article wondering about "What is the next big thing"? I just have to chuckle because whoever is writing that article is not an entrepreneur, probably, so they're not going to know. And we can't predict these things.

We invested in Netscape in '94, and everybody looks back and says, "Wow, that was really good. You invested in the first commercial internet browser and it started a revolution," and so on like that. That was a gnarly looking start-up when we saw it. We met in the conference room right over there that has all the glass walls. It was two guys. There was a young fellow named Marc Andreessen right out of the University of Illinois Computing Center, who was twenty-two and looked about sixteen. He had never developed a product before that was commercialized. Then there was Jim Clark, who had founded Silicon Graphics, yes, but he wasn't going to be full time at the company.

Kiley: Incidentally, Clark was also a cofounder of Healtheon, was he not?

Byers: Yes, when we were incubating that, we went to him with the idea and combined forces. So think about today, if a team walked in and the one full-time person is twenty-two and the other guy is a part-time advisor, well that looks like Hybritech, right?

Kiley: And Genentech.

Byers: And Genentech. And then they said, "Actually, we want to commercialize this thing called a browser, and our business model is we're going to give it away so we get big fast and get a whole lot of users, and then after that, we'll figure out how to monetize that base." Is that a fundable idea? And they didn't own the intellectual property to the idea either at the time. So anyway, these things in retrospect. So when is the next Netscape going to walk in, or the next Hybritech, or Genentech, or something like that? That's what's thrilling about this job. Nothing is obvious. It's all ambiguous and it's all pretty gnarly and pretty unfounded. No team ever comes to us fully formed with superstars.

Kiley: As a matter of fact, when you say what's next isn't obvious, that resonates with me. It is as if I were to say, "What's going to be invented next?" And under our laws, you don't get a patent on an invention unless the invention is *not* obvious.

Byers: Exactly. Non-obviousness—a very important concept. Whoever developed our patent system were geniuses, just as whoever developed our NIH extramural funding system were geniuses. So, I am excited about a new area of biotechnology that is evolving now, that people call "personalized medicine." That's a catch-all term for a variety of things that have come out of a convergence.

Kiley: Please describe the variety of things.

Byers: It's a convergence of information from the Human Genome Project. What are the various components of the human genome and how do they relate to individual cellular response? That would be: "What are the inflammatory genes? What are the growth factor genes? What are the genes that activate and regulate cell proliferation?" All of these things. This became known in the nineties. Another part of this convergence that we call personalized medicine is gene chips. The ability to analyze gene expression across large numbers. On a gene chip, you can lay down thousands and thousands of genes, and then with a patient sample, look and see what the activities are, up- and down-regulation, in the genes.

Kiley: Just for the record, you were a part of the gene chip development, were you not?

Byers: Yes, we were involved with a company called Synteni early on. It, and Affymetrix, and Motorola, and Agilent were all pioneers in that. So then you applied the gene chips. Then you apply some good old bioinformatics, like we talked about earlier—the ability to analyze huge amounts of data using algorithms and software and powerful computers. Because you'd be parallel processing all of that. Then, statistical techniques. That's nothing new, but actually some of those techniques needed to be invented to look at the comparisons of gene expression and weight them differently and compare them to biological outcome. So this is this area of personalized medicine. What does this mean about personalized medicine? This is, in a way, a little bit *déjà vu* to my walk through entrepreneurship and what to do in the late eighties. In the past few years, what I've been doing is taking a fresh look at medical practice—specifically, very difficult disease areas—and saying: "Where is the need and what is the need?" What I've been most interested in are diseases where the cost of treatment is high and the decisions about treatment are made very ambiguously. The data is ambiguous, the inputs, and so on.

A good example is cancer, where the oncologist and the patient are working somewhat in the dark. Sure, they've taken a biopsy and it's been looked at by a pathologist, and the pathologist confirms cancer of a certain stage. But so begins, then, a decision-tree process that is fairly poorly informed. What is the chance of reoccurrence of that cancer? Which therapy would be best for this patient's cancer? Not cancer of the breast or the colon or the liver, but cancer the way the cells in that individual person are activated. And then what would be the response to therapy that this patient is going through? How do you measure all these things? None of these measurements or diagnostics exist.

Kiley: For the sake of the reader, implicit in what you are saying is that the cellular responses to therapy in an individual patient may differ from the response of another patient because of polymorphisms in the respective patient's DNA.

Byers: Yes. What we have to acknowledge is that our systems are extremely complex. They have redundancies. They have back-up systems. Each of us are very much

the same—all we humans—but we’re all very much different, too. When we have disease we have different diseases. My neighbor might have colon cancer and I might have colon cancer; those are two very different diseases. But the way we have developed and defined diagnostics and therapeutics up to this point is to categorize them in the same group.

Kiley: I’m aware that Kleiner Perkins Caufield & Byers has invested in at least one so-called personalized medicine company. And its name?

Byers: Well, we’ve done two and we’re actively incubating a third. The first one is Genomic Health.

Kiley: That’s Randy Scott?

Byers: Randy Scott is the brilliant entrepreneur who came to us with this idea. It was the entrepreneur who opened my eyes to this area. I knew all of this information I just described, but I didn’t bring it all together in my mind.

Kiley: The next company?

Byers: Is XDx.

Kiley: Where is that based?

Byers: South San Francisco.

Kiley: How is it different from Randy Scott’s company?

Byers: Genomic Health is working just in cancer and is working on diagnostics to predict recurrence, therapeutic response, and so on. XDx is working in the fields of transplantation and immune system management, and is working on blood tests that will predict rejection and obviate the need for very expensive and very painful biopsies as well as tests for lupus and RA.

Kiley: You said earlier that KPCB’s philosophy is to avoid starting companies that might compete with other companies in your portfolio, and I’m beginning to understand that personalized medicine offers a rich palette of opportunities of different colors that satisfy your criterion of non-competitiveness. I won’t ask you about the third company you are investigating, claiming that’s proprietary, but what strikes me is that if you are now investing in such companies, it is because you think that personalized medicine will happen within your planning horizon, by which I mean within that period of time following which you are obligated to return profits to your limited partners.

Byers: That’s right. In fact, it’s going to happen fairly rapidly. Because these are diagnostics and there are some proprietary business strategies we have that I

won't go into, but from the time of founding to the time of first revenue will be in the range of two and a half to three years. There are ways to get to that that we think are very clever—project development strategies, clinical development strategies, and regulatory strategies that allow us to do that.

But let me come back to this convergence because I think this is something that's very important, and I'm sure a year or two from now will be done even differently than what I'm describing because more technology will be applied to it, and so on. Another piece of the convergence was the development by Applied Biosystems of the TaqMan instrument. That is not a sequencing instrument; it's an instrument that allows you to look at, in an efficient way across the set of genes, their expression patterns. And so TaqMan automated the process that allows you to look at a relatively small number of genes. What I mean by that is, we've all read about gene chips and Affymetrix did a great service to the industry and science by developing these large gene chips, and they work well for very large number of genes—6,000 genes for example, or 10,000 genes or something like that. Okay. And Synteni did that too. But what if you only wanted to look at twenty genes? What if, in your product development process, you started with 6,000 candidate genes, and as you continued to do your studies on patient samples and in clinical trials, you were able to winnow it down to twenty genes. Not a one-gene test, but it took twenty genes to get the statistics right about prediction, or prediction of recurrence, or drug response. You have twenty genes, where you don't need a gene chip—it's too expensive—but you need some other methodology. This allowed that to happen. This technology from Applied Biosystems. It came along at about the same time too.

The genius of the founders of Genomic Health is they saw this convergence. Randy Scott started this company with two executives from Genentech—one is Joff[re] Baker—who understood this convergence of TaqMan and gene expression and using data from the Human Genome Project and being able to scan using bioinformatics, all the public information databases. We did an arrangement with Incyte, where we got access to their proprietary genomic databases to know which genes were candidate genes. The other cofounder was Steve Shak, who came from Genentech, where he worked on Herceptin, and that is an excellent model for what I'm describing. Herceptin was a therapeutic antibody developed for women with breast cancer. When they ran the clinical trials it didn't turn out well. Less than 20 percent of the women were responders. That's not good. But then they had the idea, "Well, what if we tested the women's biopsy tissue to see who is HER2neu-positive, who would respond to this antibody that targeted the HER2neu? When they did, and picked the HER2neu-positive patients and then gave them, as the cohort group, the therapeutic they had a super-high response rate in that patient category. That is personalized medicine in essence. If we had to point to say maybe the first pioneer in this combo of diagnostics and therapeutics married together, it is Genentech and their Herceptin product. So, Steve Shak coming with that

methodology and working on different products than the ones he worked on at Genentech.

Kiley: So, for the reader's sake and for my own, tell me if this is not right—that one outcome of personalized medicine is that a physician can prescribe a drug for me with greater confidence that it will be beneficial to me, given my genetic profile. Another outflow of this is that companies can more readily conduct clinical trials more effectively and more economically by administering drugs only to the patients most likely to react well to them.

Byers: What I'm getting at is, you're exactly right that if this technology is converging now and becoming available, wouldn't everyone tune their clinical trials in such a way that they would test the patients going into the trial as being probable responders to the drug. Yes, but when they supply that information to the FDA for approval, the FDA, rightly so, will label that drug as only being applicable for people who meet that diagnostic criteria. The pharmaceutical company then, is faced with a dilemma. Do they reduce the cost—the number of people in the trial—and increase the probability of approval and success, while at the same time reducing the size of the market? Well, do they really reduce the size of the market? This gets to a lot of people taking drugs today for whatever indication [who] do not respond. It doesn't help them, but they still are buying the drugs. We have what might be seen as a somewhat inflated pharmaceutical industry, and it's making, building, and supplying drugs through the technology that we've had up today, to the masses, based on disease defined by location. What will change over time—and I'm sorry it's going to happen slowly—is that over the next ten, twenty years, it will come to pass that pioneers in this industry will see that they can more carefully target these therapies. That's right. Now that gets into an interesting topic. You might ask, "Well, why isn't everyone doing all of what I'm describing now?" There are a variety of believers and there are a variety of different interests. This is going to evolve over time, and I think, if we fast forward ten, twenty, thirty years from now, this is the way medicine will be practiced. My global view is this is going to turn medical practice on its head, and may be the solution to the cost of healthcare. What we have now is blue pills and green bottles. Let's start with the FDA approval process and work backwards. If the goal of a company is to get approval at the FDA of their product that they have spent eight to ten years and hundreds of millions of dollars developing, they have to prove statistical significance in their clinical trial that their drug is efficacious and safe. There's a whole statistical process to doing that that boils down to what's called a *p*-value. In order to do that, the company has to pick a set of patients they're going to test it on for safety and efficacy and so on. The lower the incidence of the disease or the response rate, the larger the trial has to be. You increase the *n* number. This is all statistics. That's why when you're running cardiovascular drug trials, you have ten, twenty thousand patients. When you're running a cancer trial, if you can show efficacy in a hundred or two hundred, sometimes you can get your *p*-value statistics.

Who will be the agents of change? I don't think this can be legislated. It's too complicated, in science. I think what will happen is that it has to be proven first. We're still in the early days of proving this. I think it will take new companies, start-ups, without the conflicts of interest, without the axes to grind who will need to develop these products and get them on the market and get them adopted by doctors and prove this out. Then the doctors, I think—and the patients, somewhat too—will start saying, "I see it. I get the light. I want more of this kind of practice of medicine." So it's my belief that the agents of change here will be the doctors, because they are motivated to do the best thing for the patient. I think the payers initially will say, "Gee, these diagnostics seem very expensive," but the more they think about it over time, they'll realize that it will have cost savings for the whole system. I think, eventually, the pharmaceutical companies will come around to the view that Genentech had, which was, "Let's develop a test and figure out who should get this drug." That's why I think the way this is going to play out—and I could be wrong—is that there will be a set of innovative new companies—and this is to answer your question about what's new under the sun in biotech—who must pioneer this, as independent companies, separate from the drug makers. And they're Swiss in a sense. I use that term to mean they stand alone and are independent, and they really are servicing the doctors.

Kiley: I would say that I agree the doctors will be the agents of change, but first, the entrepreneurs—of necessity—will be the agents of change. What you've been describing strikes me as the perfect example of the creative destruction of the entrepreneurial process, in which the artifacts of past times are moved out of the way by newly evolved animals that are not married to the past or to past practice, but are able to write on a clean slate. Now, you have said that you see medicine changing as a result of these convergences in ten or fifteen, twenty or perhaps thirty years. In the meanwhile, the companies being formed today have got to have sustenance. Are you describing a first stage in which modest returns and modest products will sustain these companies until the big jackpot comes into view decades hence?

Byers: I'm very optimistic we're going to have near-term success with these companies we are starting. I was waxing enthusiastic about something that I am not qualified to predict on, but I do anyway, and that is huge change in the health-care system. I give those longer timelines because I have a lot of scar tissue in and around changing physician behavior and changing the reimbursement behavior of payers, insurance companies, and Medicare. It'll take a long time. Also, changing pharmaceutical company behavior. But I think this will happen. I wouldn't be involved in these start-ups if I didn't think we have near-term prospects. I'm hesitant to give revenue projections, but I think that should some of these products work out—these expression diagnostic products I'm talking about at GHI [Genomic Health, Inc.] or XDx or another one we're incubating in another disease area, and then there's a fourth disease area I'm interested in, too, once we have some time to work on that—these diagnostics can sell for

attractive prices for diagnostics. A lot of diagnostics sell for \$30, \$40, \$50. Diagnostics are the second-best bargain in healthcare. The first-best is vaccines, but diagnostics are always, in my mind, very under-priced for value, for what they provide. If they can provide an exquisite answer to what is wrong with the patient, then the solution usually will be targeted, and that's always better.

A simple example is infectious disease. If someone has an infectious disease, and there's a diagnostic to say not only what kind they have—viral or bacterial—but which is the right antibiotic to give them that is not resistant in that situation there, then that patient is going to be fine very quickly. That's a simple diagnostic. These that we're talking about developing, are priced \$1,000 and up. The initial response by some people would be, "Well, that's a staggering price," but if it drives the decision of therapy—or even device implantation—of fifteen, twenty, thirty thousand dollars, that's good economics. It's incumbent on the entrepreneurial companies to prove that health-care economics, to do the analysis and show that all told, when you run down the decision-trees of cohort groups of patients and what happens to them, that it turns out well. Cardiovascular is an interesting area. How is it decided that a patient gets a pacemaker, or a defibrillator? It's decided on fairly gross and rudimentary measurement tools, and then those are expensive solutions.

Kiley: This ends Tape 4 Side B [sic].

[End Tape 4, Side A] ##
 [Begin Tape 5 Side A]

Kiley: This is the second interview, Tape 5 in the Byer series, Side A, October 2, 2003. The time is 2:33 p.m.

I'm getting the impression that you don't think your run is over in biotechnology venture capital, rather that there is lots more to do in that area. I wonder if you think there's enough left to do that young people could today aspire to careers in venture capital in biotechnology. Let me put the question to you this way: If you were to approach Kleiner Perkins Caufield & Byers today with the credentials you held at the time you began work with Tom Perkins, would you be hired?

Byers: No, I wouldn't be. In fact, I was not qualified to do biotech venture capital in the late '70s, early '80s from the perspective and knowledge I have today. I was an undergraduate degree in electrical engineering, you'll recall, masters in business, and had worked for a few tech companies, and then in venture capital, and then met Ivor Royston and Howard Birndorf, and we started Hybritech. They knew what they were doing in the lab. I had no idea what I was doing there. I was just inspired by Bob Swanson and the starting of Genentech to want to do something like that.

Kiley: Was the bar lower for venture capital entry in those days?

Byers: Yes, it was. It's hard to imagine today, but back in the 1970s, venture capital was not a known profession. It wasn't popular. All my friends who were popular were in investment banking, management consulting, and real estate development. So, no one really, except myself and a few other people, wanted to be a venture capitalist. It was kind of a 'nichey', kind of backwater kind of financial profession—not to us, but in the grand scheme of things. Now it's been so over described and so over written about and gotten so much notoriety, I think venture capital is now blown all out of proportion. We are in fact, a service provider to entrepreneurs, just like accountants, lawyers, and so on.

But back to your question about qualifications, it's all changed today. Why is it changed? It's because, one, the depth of knowledge of the technology and what we call domain expertise is so complex that in order to even have a credible conversation with an entrepreneur, a venture capitalist has to be steeped in that specific industry in a very deep way. There are several ways to get that. Tom, you could qualify as a venture capitalist today in biotech, because you have a deep domain expertise in the science and technology, intellectual property, you've been around a bunch of companies, you've been on boards, you were in the management team of Genentech, and all of that. You have true value added. We like to say around here now at Kleiner Perkins, one "earns the right" to advise an entrepreneur. One doesn't have the right because you have money, or stature, or reputation. You earn that right. When entrepreneurs come to Kleiner Perkins, or any other venture capital firm, they might come because the firm has a good reputation, but they come to a specific partner. If someone is starting a new enterprise software company, they're probably going to come to see Ray Lane or Ted Schlein. Ray built Oracle, and Ted built Symantec. If they come here with a biotech company, they're probably gonna come see me because I've been around the block, but if I didn't have that, I wouldn't be qualified.

How can someone get those qualifications today? One, it would be a deep educational background in these industries.

Kiley: In the industries, or in the sciences?

Byers: Well, I think starting with the sciences, and then in the industries.

Kiley: So would Alex Barkas be an example of that?

Byers: Yes. Well, Alex was a partner here, and now off running his own venture capital firm. He has a Ph.D. He has a deep knowledge of the science and has always loved that. Alex never worked in a company, so he didn't have the industry expertise, but he's learned that along the way. He got in venture capital ten years go. Today, someone with just a science background can come into a venture capital firm, but it would be a risky move without that industry experience. If I

had to do a prescription for a path a young person might follow, it would be something like this, by example. Not exclusively. Something like this: In biotech, it would be undergraduate degrees in biology, molecular biology, biochemistry, something like that, at a great university. The best the person can figure out. I am not a believer that only the elite private schools or something like that are the way. You can get that anywhere. Michael Bishop, chancellor of UCSF, Nobel Prize winner for oncogenes, undergraduate degree was from Gettysburg College in Pennsylvania, and here this guy is a genius. So, any place like that. Then, go on to graduate school at some place like UC San Francisco. It, with its combination of basic science and its clinical work, that remarkable ability to tie lab to bedside clinical experience and translation, I think is a fabulous rounding out of PhD/MD or even an MD or something like that. UCSF's new Mission Bay Campus that's just being built in 2003-3004, is, I think, going to have a world-changing effect on medical research and practice.

If someone is interested in devices, get an undergraduate or graduate degree at a place like Duke or Georgia Tech or Stanford in biomedical engineering, where they marry the engineering school and the medical school into a new kind of convergent department, and the students learn electrical engineering, biology, molecular biology, biophysics, and solve problems that way. Then, I am a big fan, before people go into venture capital, of going to work in a company. It's back to this: How do you assist entrepreneurs, which is 99 percent of this job. Writing the check is one percent. Ninety-nine percent is assisting the entrepreneurs in the next five to ten years building a company. How do you do that if you haven't been there and don't know it? So, to the extent possible, get a job in one of the well-run companies, whether it be Genentech, Amgen, Gilead, MedImmune, Biogen-IDEA. Or in a large pharmaceutical company, too, is fine.

Kiley: And you would think either of those is superior to a job in a start-up?

Byers: Well, I do initially, unless the young person is either lucky or a genius at picking the right one. If the start-up goes on to be a huge success in five years, and that person rode that rocket ride—a great experience—but the chances of a young person picking that is slim. I've seen in the past five years when we went through this bubble, and the bubble was not just Internet, but it was telecom and software and biotech too, so many careers of young people screwed up and taken off in the wrong direction, and so much disappointment. They heard the siren call of entrepreneurship and joined those companies, and those companies don't exist, or they got laid off. Then, what does their training and résumé and career path look like? It looked like they got well educated, and they went to a young company that doesn't exist anymore and no one knows the name of. What mentorship, what training, what coaching did they get? I think this is all about the basics.

Kiley: You mentioned Mission Bay and your view that it will have a profound effect on the development of biotechnology, presumably in the Bay Area. The Bay Area is

already strong in biotechnology. What are its advantages, relative to other regions of the country, if any? And are there regions of the country that now bid fair to compete well with the Bay Area for biotechnology prominence?

Byers: You know, I'm not a regionalist, or think that science or entrepreneurship belongs [to]any one place. I'm not loyal to any one area. I'm loyal to the planet.

Kiley: Well, that's very praiseworthy of you.

Byers: I don't know about life anywhere else, but if I knew about life there, I'd be loyal to that too. My uber-goal is to improve life as we know it. Where inventions are made, I don't care. The great thing about healthcare science is, it hasn't cared either. Unlike other technology areas, the healthcare medical science has this tradition of sharing breakthroughs, sharing knowledge. It's published. Scientists go to conferences and stand up and talk about their work.

Kiley: For having said all that, your partner Tom Perkins has told me, that a time came when he had no interest in investing in companies that he couldn't get to in his automobile. With some notable exceptions—I expect Millennium Pharmaceuticals is one of them—I would bet that you have a preference for investing in local companies. True or not?

Byers: That's true, but that's just a personal lifestyle choice. Let me get back to that in a more serious way.

Kiley: Well, is it, or is it also a function of your belief that a venture capitalist gives best value if he's proactive and available on site at the company?

Byers: Oh yeah, that's all part of it too. I think what was in Tom's statement, probably, and in my preference for local companies is that, if I'm spending two days to get to and from a company every time I visit it for a day, that's pretty inefficient. If they were all local, I could do two of three as many companies, or do two of three times the number of visits. Assuming that my visits are valuable to the company, then all the better. The great thing about San Francisco Bay Area—and this was luck for me—is I happened to be living here, this is where it all started, and I'm still living here. There's plenty to do. There's no need for me to go do this anywhere else. I think that a venture capitalist sitting in San Diego, Seattle, Boston, New York metropolitan area feels the same way. There's no, really, need for them to go traveling all around, although a lot of them do. A lot come out here, but that's because we have a longer history of entrepreneurship here. A lot of entrepreneurship is driven by inspiration by others who have paved the way in a sense, and networks of people, and so on, like that.

The Bay Area has, like Boston and other areas, a great culture of risk-taking, so I want to come back to that. Where is it okay to take risk? I think this is why Europe has lagged the U.S. in biotechnology companies and startups. It's not

that Europe didn't have the technology. In fact, they had a lot of technology well ahead of the U.S. Monoclonal antibodies were invented in England. They just didn't believe they should patent it, and no one there bothered to start a company around it for a long time, until the example was shown by Hybritech and Centocor and others here. So I think it's all this kind of mix. I think it's grand that other areas have developed in biotech for my uber-goal. Now, I don't want a lot of companies started in personalized medicine, so I'm going to contradict myself there, and say that my hope is that there aren't too many competing companies started.

This gets to: Are there too many venture capitalists? Yes. I think there are too many venture capitalists. I know that sounds self-serving, and that I want a more exclusive small group in this, but what I mean about that is I think it's pretty easy to look at the number of fast-follower companies that happened in each technology and product area to see that there are probably too many venture capitalists because there are too many people who, when they see something good and they can't invest in that company, they want to have one of their own. So they go out, and they kind of cobble one together, or invest in the next one they see.

Kiley: Is it a corollary to too many venture capitalists that there is too much venture capital money chasing too few good deals?

Byers: Yes, and we're coming off a period where there was too much money that came into venture capital business. The venture capital business I go back to is a niche business. It is a very valuable service to the economy and innovation and all these things, but it doesn't scale. At ten partners, we are—relative to the seven hundred firms in venture capital in the United States—we're large. It's just not a scaleable profession.

Kiley: Why not?

Byers: It's a profession about applied judgment and wisdom and advice. It's not a profession about money, per se.

Kiley: Does Vinod Khosla really need your advice when he forms a new company in the optical components field or telecommunications? Does John Doerr really need your advice when he forms a new company in his particular niche?

Byers: That's an excellent question. My advice in the domain decisions they make in those specific technologies: No. Do we here in this firm believe and have proven over time that group decision-making is better than individual? Yes, because so much of this is ambiguous. It has to do with judgments. In the life of a young company in the first few years, there are usually a couple of really pivotal turning points, where a company has to decide: "We have three projects, we can only afford to pursue one; which one is it?" "We've been going after the

commercial market. It's on its face right now in telecom. Should we turn the company toward government markets for the next year or two or, with those long purchasing cycles, would that be down?"?

Kiley: Let me see if I can set this—

Byers: And so on. The ability to bring these problems to your partners, in a Monday partner's meeting, and sit there unrushed for an hour or two or three and discuss them, always turns out to be what I would call "the partnership process." I'll take problems into the partner group, that going in, I think, "Well, I just need to talk about it. Maybe they'll be my therapy group and if I talk about it, maybe the answer will come to me." I am still surprised by how—even though they don't work in my industries, and I don't work in theirs—they come up with a solution I didn't think of. That's about a team problem, or a strategic shift, or one of my companies is negotiating a deal with a large pharmaceutical company, and I'm thinking traditionally. They go, "No, have you thought of carving it up this way? Have you thought about doing that differently?"

I taught them about corporate partnering. Biotech and large pharma started corporate partnering . Genentech's corporate partnering deals that you did in the late seventies, early eighties were never done in the technology industries. One of the things our firm was able to do because you worked with Tom Perkins, and Tom taught the rest of us, is teach that to all of other partners. Now, partners like John Doerr and Vinod Khosla, Ted Schlein, and others, for a decade plus have had these networks of companies we built with other large, huge companies in their industries, and these alliances that were built. This all came out of this model.

Kiley: What you say about your Monday partner meetings sounds a little bit to me like a peer review process—the kind of process that ensures quality science in companies that publish and peer review journals. Is this right, that if John Doerr or Vinod or Ted Schlein can explain to you why an investment should be made in a domain outside your expertise, then they could probably explain it to one of your limited partners, as well? If it succeeds, you don't have to explain it to the limited partner; but if it fails, he probably would like to know enough about it to understand why you made the investment. Is there anything to what I'm suggesting? Put another way: when you take an investment proposal in biotechnology to your partners who have no expertise in that domain, do they cross-examine you fiercely?

Byers: They do. It's always a surprise to me, and you think I would have learned by now, when I take it to them how down in the weeds and at the nanomolecular level, I have become about that start-up I want to get done, and how emotionally I've bought into it by the time I take it into KPCB's big room with the team on a Monday afternoon at two o'clock. Up to that point, I've worked the hallways, and shared the diligence and so on like that. We don't make a decision on the

spot, necessarily. We'll discuss it. They'll give me more homework to do, and I'll go away and do that. We all do this here. We all do it to each other. We senior partners who've been around here a long time, we're careful to have our process of approval to be the same as the newest partner, because that empowers the culture and the process. But yes.

And what would they come up with, you're probably wondering? Their instincts of looking at a founder and knowing the proportion of the founder's thinking that is driven by what is the science capable of doing—what can be done from the science. Them seeing a little more clearly and objectively than me—or sometimes a lot more—that there was no marrying of what the market might want or need to that. In biotech, so many times what we do is, since it is science driven and most of the risk is in the technical risk, that's all we focus on. "Okay, with the convergence of these pieces of technology, we can—wow, look what we can do. We can come up with something like *that!*" We tend to kind of usually take for granted that the rest of it will work out. My partners, who come from these other industries, they don't take all that for granted. They start asking some pretty tough questions about, "Well, what would be the channel of distribution for this?" "Look at these revenue projections. How did you get that? What is the rate of adoption? Did you go interview some doctors? Did you go interview pulmonologists so that they say that they would adopt this new inhalable drug? What is the measurable figure of merit? How was the decision made by this customer?" This is a classic they do—"Okay, you know, I get the gestalt for it. Let's take one customer. Give me the whole economic analysis of one customer."

In software, they do that all the time. They look at one customer and say, this customer buys the package of software, and the recurring revenue, upgrades, maintenance and service fees. Then there are some professional services on top of that on all of that. What is their ROI? [Return on investment]. They look at one customer, and if it pencils out, that makes sense. We, in biotech and medical device—Joe Lacob and I talk about this all the time—we don't think that way. Our partners force us to do that, and sometimes when you do that and you boil it down—let's go back to personalized medicine. That one oncologist sitting there with one patient, making decisions—what is the economic framework around those decisions?

Kiley: Very complex.

Byers: Then you take that and explode it back and decide if it's a good thing.

Kiley: Your mention of Joe Lacob reminds me that a time came, here at KPCB, where either you de-emphasized biotechnology, or shall I say, you chose to emphasize something else more—internet, telecommunications, so on and so forth—and I gather that you are, at least in your individual practice, back to biotech. Very plainly so. In the course of your de-emphasis of biotechnology, the life science

complement here at Kleiner Perkins shrank by several people. Do you intend to grow it at this stage?

Byers: We do. There's been a lot of curiosity about what we do and why we do what we do. You know, this profession and doing biotech with these long lead times, it's a marathon. It's not a sprint. The investment rate per year in any one industry is not a good measure of either commitment or interest. We don't want to be any bigger firm than ten partners, so we did a lot of biotech. Because we won't do competitive companies, there are periods of time where we may not do a lot of activity, because we are not going to do another company in the same space of one we've done. When you've been doing it as long as we've been doing it, sometimes what we've got to do is wait for a new revolution in technology to where we can find some new things to do. Also, we're not a driver of the process—it's entrepreneurs coming to us—and sometimes we have dry spells. I think the mid-nineties, around '95, '96 for us, was a lot of things happening at once. It was those two things I just mentioned, and we just had had an unbelievable experience with Netscape. So I went off and incubated two new companies that had something to do with healthcare but something to do with internet. I found that intellectually interesting to do. There's only so many hours in the day, and these were start-ups started in this office with me as the founding president.

Kiley: Healtheon was one?

Byers: Healtheon was one, and the other one was Drugstore.com. Both of these companies are turning out to be successes—spectacular successes—and have endured, and all the competitors have fallen by the wayside. This was a lot of work to do this. Also, another thing going on about that time was there was a wave of proteomics company start-ups. I didn't believe in proteomics as a business model as a reason to found companies.

Kiley: Will you tell the listener what a proteomics company is?

Byers: Well, there were genomics companies, and the business there was selling the information about what is in the human genome—the sequences and so on. Subscription databases and so on, like Celera and Incyte were. The next wave of companies were companies who said, "Well, we can now define which proteins are made or enzymes were made from all of these genes." But what value was that? It was interesting information and it was more targets. As we talked about earlier, I didn't think the world needed more targets. What the world needs is more drugs. So I decided to wait that out.

[End Tape 5, Side A] ##

[End of interview]

Interview 3: June 15, 2005

[Begin Tape 6, Side A]

Kiley: This is tape 6, side A, of the third interview of Brook Byers. It is 3 p.m., June 15. We are in the offices of Kleiner, Perkins, Caufield, and Byers on Sand Hill Road in Menlo Park. Good afternoon, Brook. When we last spoke, you told us about your focus on personalized medicine, mentioning amongst other things a company called Genomic Health. I wonder if in the ensuing year, year and a half, you have continued to believe in the importance of that as a focus of your efforts and, if so, can you bring us up to date on what has transpired, what other companies you have invested in, and so on.

Byers: Sure, Tom. It's hard to believe it's been a year and a half; time has gone by quickly. And in that year and a half, I'm happy to say that personalized medicine, and molecular diagnostics as a component of that, have developed into a broadly supported and discussed area. The whole area of personalized medicine now has grown to encompass not only diagnostics but also a way of thinking about how therapeutics will be developed, and we can get into that in a few minutes. And then very creative thinking by scientists and entrepreneurs about viewing medicine from the patient looking outward, instead of the way drugs and so on have been developed to this point.

To update you on Genomic Health, a year and a half ago it was still in quiet mode. It has now launched its first product, having completed clinical validation trials—three of them actually—that showed that the first test for breast cancer patients actually had the ability to predict who would be a recurrent breast cancer patient over a ten year period and who would be very unlikely to be so. And also in the clinical trials, what came out was that the biology of the individual tumor of patients showed who was highly likely to recur. And, it turned out that the tumor biology spoke to which patient is most likely to respond to chemotherapy. All this tied together so that the oncologist and the patient, sitting together, can decide to have the tumor biopsy in paraffin-embedded format sent to Genomic Health's lab, the tests run, the information sent back to the doctor. Then the doctor and patient can sit and look at these index and probability scores and make a rational decision with data on whether or not the patient should have chemo[therapy]. That contrasts with the format today, where the decision is made basically on age, size of tumor, maybe some family history, which isn't much to go on. Genomic Health is also already now developing products in R&D phase for other cancers for men and women.

A year and a half ago, I mentioned another company that was in R&D phase. It was XDx, shorthand for Expression Diagnostics. And XDx is applying the techniques of looking at gene expression and molecular diagnostics to immune system measurement. What I mean by that is with a blood test being able to break down the components of the immune system and see activity. The first product they have already now launched is for organ transplant patients. When a patient gets an organ transplant they then have to come back in monthly to the medical center and have a tissue biopsy taken. In the case of a cardiac transplant patient, that is done by a fluoroscopy procedure, which means exposure to imaging agents in an individual cardiology lab. It's very painful, very awkward, takes a long time, and a catheter is inserted down the neck carotid vein into the heart and a piece of tissue is taken. XDx's product is a blood test that not only will give as good an answer as that tissue biopsy would, but actually will see rejection ahead of time. Why is that? Well, it's because by the time a biopsy would show tissue damage of immune rejection, the damage is already done. But by looking at gene expression of the lymphocytes in the patient's blood, you can actually see it coming—certain genes will be up-regulated.

Kiley: And in that case can you intervene therapeutically to fend off the damage?

Byers: Exactly the point. You can intervene earlier and therefore with less drug. They will work on other products at XDx into other immune diseases. Well, what about rheumatoid arthritis? It is another case where by the time the patient is experiencing the flare and goes to the doctor and gets very expensive drugs—and thank goodness there are drugs for that today—Humira, Enbrel, Remicade, others like those—then the patient needs high doses. Well, imagine what would happen if through simple blood tests you could see that flare coming in advance and then give less drug. So all of this has a good health economics outcome too.

Kiley: Do you think that XDx will wind up marketing its own products?

Byers: Yes. In both the cases of Genomic Health and XDx, they will have their own sales forces calling on the specialists. They have a CLIA lab at their facilities, so the samples are sent to them and the tests are run there to ensure high quality and consistency.

Kiley: My understanding is that marketing diagnostics is a notoriously difficult business for a small company to crack into. How do these companies overcome that obstacle? Is it simply a matter of the great need for their tests and their unique character?

Byers: Well, we think there's a great need for the tests, but the medical community is conservative, and so the time to adoption by the medical community of any therapeutic or diagnostic is a long time. What makes this business model work is that these tests are aimed at specialists, so there are fewer in number. So instead of 25,000 general practitioners and doctors' offices there are a few thousand

breast cancer oncologists, a few thousand immune system experts, or in the case of organ transplant, there are a few hundred centers in the United States, a hundred centers in Europe, and so on. So a small dedicated sales force of fifty can handle that.

Kiley: Harking back to the breast cancer diagnostic you mentioned in the context of Genomic Health, is a model for that the Herceptin product of Genentech with the associated diagnostic that lets one predict whether the patient will benefit from the product?

Byers: Yes. That was the pioneer of this way of thinking, as we discussed in a prior interview.

Kiley: Does the Genomic Health product help the patients that are not helped by Herceptin?

Byers: Yes. It's independent of the Herceptin decision. The Herceptin test will see if a patient over-expresses the Her2/neu gene, and if so, then Herceptin is more applicable, and I think that's roughly twenty percent of patients. Those patients still need to decide about chemo or not.

We have another new company, in this theme of molecular diagnostics, called CardioDx, and it's working in cardiology and on sets of problems that we've observed from doing a lot of primary research with cardiologists about what are their most difficult decisions that result in expensive therapies. An example of that are implantable defibrillators. It turns out that less than half of the people who have a defibrillator implanted in their chest, and leads put into their heart, ever have that defibrillator fire, so it does no good. Whereas roughly a third to a half of the patients who discussed having the defibrillator with their doctor, but for one reason or another decided not to, die of sudden cardiac death from an arrhythmia. So this is an opportunity where obviously the decision-making process is not working well, because right now the decision is made on an abnormal EKG, or ejection fraction, or something like that. But it's still a hit and miss. And if you forecast forward, the only real solution to trying to get around and stop that huge number of sudden cardiac deaths from arrhythmia is implant more defibrillators. But this is where the whole idea of personalized medicine is empowered again, which is, let's look at it from the point of view of the doctor sitting with the patient, how do they make a decision of what is the best therapy from the armamentarium of drugs and devices coming at them.

Kiley: Is CardioDx a company that you inspired, or did the founders come to you having identified the need and bearing a prototype solution?

Byers: That was one that we thought up ourselves.

Kiley: You identified the need, and then went looking for the solution?

Byers: Yes. Now that we've been in this mindset, we started thinking about what are other clinical areas where we could apply our methodology, and then we got a working group together, and hired some market researchers, and we spent nine months interviewing cardiologists, with a lot of blind alleys and some elimination, and came up with three product projects that we are working on. And then went to scientific meetings, cardiology meetings, studied the literature, talked to a lot of world-famous researchers and cardiology researchers, and finding out who knows what about these areas, and then got lucky along the way.

Kiley: Do you realize how much what you just said diverges from the laymen's view of what it is a venture capitalist does? It's remarkable. That's very impressive.

So, what is the nature of the putative solution to sudden coronary events? Is this a diagnostic, is it a diagnostic device, is it based on molecular biology? What can you say on that score, if anything?

Byers: Well, it's early days; we're still in the R&D phase, and like a lot of R&D, it may turn out it doesn't work. But if it does, if our theory is right, what we're testing for is the presence of polymorphisms in the genes of individuals, common sets. We believe we have found abnormalities in a certain number of genes, less than a dozen, that would show up in a blood test that would indicate which patients are more likely to suffer this and therefore need it to avoid cardiac death from arrhythmia.

Kiley: Are polymorphisms at the heart of most personalized medicine opportunities you see ahead of you?

Byers: Not necessarily. The tools to look at disease in an individual first are expression diagnostics, looking at gene expression profiles and patterns. That's done using TaqMan, which I mentioned in the prior session, or gene chips from Affymetrix and Agilent and so on. Another thing is looking at polymorphisms using chips from Affymetrix or actually sequencing techniques, and the cost of sequencing is going to come down.

Kiley: Referring to DNA sequencing?

Byers: Yes. You know, it's possible to look for something in someone's genome without sequencing the whole genome if you know where to look.

Kiley: And we know where to look because of the Human Genome Project?

Byers: Yes, we now know the general road map and the locus of things.

Kiley: Ain't Life wonderful.

Byers: Mmm-hmm.

Kiley: That's life with a capital 'L'. What else would you like to say about personalized medicine? Have you other initiatives underway?

Byers: We have a company that's new—and sorry to invoke this again, but they've requested to be in stealth mode—that's working on a very low-cost, very rapid gene sequencing system. This has been the holy grail for thirty years. You and I know of prior attempts at this through Parallel Systems and so on. This company is applying nanotechnology to the problem by creating twenty-nanometer wells in materials and uses of lasers to interrogate what's going on in those wells, then putting biology reagents in those miniature wells, and putting a DNA sample into it and having the reagents sequence using Mother Nature's techniques, having reporter fluorescent tags in there. And so it's a combination of molecular biology, biology, chemistry, surface chemistry, optics, computation, all brought together. It's a fascinating, fascinating project and problem.

Kiley: You seem to have brought together some people to help you with this. I see that you've added a distinguished partner with a Ph.D. in immunology, you've also added a partner who was a pioneer in nanotechnology. Have they been involved in these several efforts? How do you see them working together in the future as nanotechnology and biotechnology converge?

Byers: Well that's a good observation that we thought was clever and almost unique on our part, and you are one of the first people to view us from the outside and put it all together. So that's true. We have expanded the team actually significantly recently, because we are seeing a lot of opportunity in the traditional biotechnology and medical device areas, but also in a nontraditional way. And so we felt that now the time was right to gear up with more capability within the firm here in partners, and I'll walk through what we've done in that.

I've been here thirty years doing biotechnology and medical device and instrument start-ups. Joe Lacob has been here fifteen years doing the same, moving more toward medical devices over the past decade, very successfully. Then two years ago we added Dr. Risa Stack, who has a Ph.D. in immunology from University of Chicago; she got it in Jeff Bluestone's lab; he is a celebrated immunologist and now at UCSF as head of their metabolic and diabetes research programs. Just recently we added two more senior executives who come out of industry. One is Dr. Beth Seidenberg, who was global senior vice president of product development and clinical and regulatory at Amgen; she did that job before Amgen at Bristol-Meyers, and earlier in her career was at Merck and the NIH. And we also added Dana Mead, who just before joining us two weeks ago was president of the vascular interventional devices division of Guidant Corporation. The vascular interventional division here locally made stents, catheters, balloon catheters, products like that, around 1.3 billion dollar in

revenue in his division. So what Beth, Dana, and Risa bring to our work—and then Bill Joy, who you alluded to, who was chief scientist at Sun beforehand—

Kiley: Sun Microsystems?

Byers: Sun Microsystems, yes, where he developed the Java language and many other things, and also is a broad intellect across all technologies—is we have added depth of operating experience, and knowledge of products, and knowledge of the industry and what's going on out there. Bringing them on has given us a better view of how it's all becoming integrated and interdisciplinary. Let me give you an example. Medical devices are no longer pieces of metal that are put in the body or used for surgery. Medical devices more now contain an electronic and signaling component, a data collection component, maybe even drug delivery and involvement with pharmaceutical components as well. The drug companies at the same time are realizing they cannot think of themselves as blue pills in green bottles or injectable proteins; they have to think of themselves as integrated into the system of delivery or devices, so that's a whole consistency. And if we go back to personalized medicine, think of the amounts of data that come out of all of these tests that are run and prediction algorithms. So that ties into computational systems as well.

Kiley: So you've built an interdisciplinary team around life sciences here at Kleiner Perkins. Do you see the same thing happening at the same level in the major pharmaceutical companies?

Byers: I don't know. I know they're talking about it. The rate at which they're moving to it, I don't know, because they keep their plans pretty quiet.

Kiley: Is it possible that they are relying on small companies of the kind that you and other venture capitalists bring forward to provide the tools that will let them use their drugs more intelligently?

Byers: Well, that seems to be the case so far. The large pharmaceutical companies are very curious about our molecular diagnostics companies and are sending teams out to visit. From what we can tell from the conversations, it looks as though they think it's important. They realize it's very hard to do, that they may not have the skill sets there because it's interdisciplinary, and I think they're taking a wait and see attitude. The large pharmaceutical companies I think also have a structural business fear, namely that if you take personalized medicine and molecular diagnostics to its logical conclusion, it would stratify markets into smaller subsets, and therefore "blockbuster products" would not be that in a traditional sense.

Kiley: But it may also reduce the cost of clinical trials to the point where a company doesn't require a traditionally defined blockbuster product in order to recoup its research investment and make a decent profit.

Byers: Exactly. So now we're getting into predictions. It seems sitting here in 2005 that the business models of the pharmaceutical industry have run as far as they can go. The only way they seem to be able to grow sales and earnings to satisfy some outside expectations, such as Wall Street and so on, is by merger, but there's an end to the possibility of doing that. The question will be: Who will go through the painful period of resetting the way they do clinical trials and looking at market sizes? And it's easier for smaller companies to do that.

Kiley: I'll turn to that in a moment, but first let's talk about acquisitions. If major pharmaceutical companies lack the skill sets required to do these things, one possibility is for them to acquire those technologies through acquisition. Do you foresee, in that event, a competition between the major diagnostics companies and the major pharmaceutical companies to chase the start-up companies that can bring these technologies to the fore?

Byers: Yes, I think so. There are not many major diagnostics companies. It's up to this point been a consolidated industry because it's a difficult business to be in. The prices for diagnostics generally don't reflect their value to the health care system; specifically most diagnostics are priced under a hundred dollars per test. So to get to scale and have an efficient sales and distribution system, it requires a lot of products, all in one system. So we have large companies like Labcorp and Qwest, Abbott Diagnostics, and so on.. A prediction would be that this is going to change. Now whether or not it's the pharmaceutical companies who move back to wanting to have a diagnostics division, like many of them used to but then they got out of it, or is it going to be the newer diagnostics company start-ups, see who gets to scale, and then they acquire others and build large mass? This has yet to play out. I'm an optimist; I like to think that it would be the latter scenario, but it'll take five years for this to roll out. A wildcard in here is, will the large pharmaceutical companies embrace molecular diagnostics around one of their products, or will the molecular diagnostics companies be independent completely of large pharmaceutical companies, and they just operate in an independent mode?

Kiley: You talked about the importance of having a full bag when a diagnostic salesman visits a potential customer, but earlier said that XDX and Genomic Health will be taking their own products to market. Do you foresee them having within their planning horizon a significant portfolio of diagnostic products, or must they go out and sell their products as one-offs?

Byers: Oh, a portfolio, yes.

Kiley: And it's within their means to build that portfolio?

Byers: Yes. And should be launching a new product per year.

[interruption]

Kiley: Brook, let me move if I may to another subject very much in the news these days, and that is embryonic stem cells, adult stem cells, and regenerative medicine in general, particularly topical in view of the controversy surrounding and press attention to California's Proposition 71, which proposes to provide three billion dollars over the next ten years to fund efforts in regenerative medicine in California. Tell me if you had any involvement in the passage of Proposition 71.

Byers: Yes, quite a bit.

Kiley: Can you first tell us what is it about the issue that peaks your interest?

Byers: So when stem cells were discovered and named only a half-dozen years ago, this felt very much to me like the same thing, the same breakthrough. This science should be pursued. In my belief, it is very important to pursue it for the benefit of mankind. In August of 2001, when President Bush by administrative order limited NIH funding for embryonic stem cell research, this to me was a remarkable and infuriating intrusion into the scientific process, because the NIH is a wonderful system where all taxpayers in essence contribute into the system to do basic research through a peer review grant system for the benefit of all taxpayers and their families, all citizens in the U.S., and the world. We humans are all in this together, vis-à-vis disease. So with that being the restriction, I was overjoyed to find a group of people who had put together this idea of an initiative on the California ballot. It didn't have to exist; it didn't have to happen. If the NIH were operating in its normal capacity and way, it would be funding embryonic stem cell research, and that'd be fine. But with the current administration's restrictions being on, it looked as though this was the best way to go forward in order to move this science ahead. California as a state fortunately has the infrastructure of science and research in universities and scientists where it can take on something of this scale and endeavor, because of its fine institutions: in San Diego, the Salk Institute, UCSD, Scripps [Research Institute], the Burnham Institute; in Los Angeles area: UCLA, USC, City of Hope, Cedars Sinai; in northern California: UC Davis, UCSF, Stanford, UC Berkeley, UC Santa Cruz. I could go on and on. I've probably left off some really great ones, too. Well, I go back twenty-five years to the discovery of recombinant DNA, and I was lucky enough to be part of that revolution. I was there when the concerns were raised about the ethical, and legal, and safety issues of that technology and how it should be rolled out and how it should be observed and monitored and regulated, and in that case everything has turned out well. This is reminiscent of that to me, and when I look back over the past twenty-five years and see the effect recombinant DNA has had not just on the biotech industry but the pharmaceutical industry and basic research and understanding about human disease and human life and human development, it's hard to imagine that we would have not pursued it.

[End Tape 6, Side A] ##

[Begin Tape 6, Side B]

Kiley: This is side B of the first tape of the third interview of Brook Byers on June 15th, 2005. Brook, you were saying?

Byers: So the state of California has the scientific and university and clinical and hospital infrastructure to absorb this level of funding. Now, over a ten year period, the question was, "How much funding would be required, should be required"? The way to think about it is that it's \$300 million per year. In the early years a lot of that money will be spent on building new research facilities, because one has to plan right now that you cannot co-mingle federal NIH funding with any other state or private funding of embryonic stem cell research. Another consequence of President Bush's ruling is that one is not allowed to use any NIH funding in a facility that otherwise does embryonic stem cell research. So that's an inefficiency. But a lot of the early money will also be spent on training of new scientists. One problem with this wonderful and exciting field of embryonic stem cell research and stem cell research in general is the best and the brightest young people are not going into it, because when they go to choose their careers, why would they choose a career that looks like it's surrounded by political issues and lack of leadership from their own government, notwithstanding the fact that other countries seem to be having a policy that encourages full stem cell research. And so that's why you get announcements like you do out of China, England, Singapore, India, and so on.

So I signed up for this campaign for all those reasons, and it was a remarkable process. Getting a proposition on the California state ballot for a November election requires 800,000 signatures. Those were obtained plus another 400,000, so 1.2 million in total. The polling all along the way showed broad-based support, from Republicans, Democrats, Catholics, Buddhists, whomever. The survey showed that every California voter has someone within their close family or once removed, say by marriage, that had a disease that could benefit from stem cell research. And those of us in the scientific community who have been around in trying to develop cures and treatments for intractable and terrible diseases realize that we're missing tools and capabilities for a lot of these diseases we can't get to yet. Sure we have drugs to reduce cholesterol, or drugs to manage congestive heart failure, or we're starting to make some progress in cancer. But for things that are neurodegenerative, like Parkinson's, Alzheimer's, terrible auto-immune diseases like diabetes, injury like spinal injury, we don't have the useful tools. We've been trying for thirty years; we're not making enough progress. It's early days; but it looks like stem cells could be applicable to those medical needs..

Kiley: Tell me first your views on the applicability of adult stem cells and stem cells derived other than from embryonic blastocysts. Obviously, the current administration would prefer that stem cell technology confined itself to cells other than embryonic stem cells.

Byers: Well, here I rely on the experts, the scientists, who advise me. I have a lot of consultants and advisors as well as partners who have a science background and study this. What I'm told is that adult stem cells are attractive because they're stem cells that we as mature differentiated adults produce. And that's true, but they have limited application. By definition, if we're producing them as an adult in some part of our body, in our brain, in our heart, in our bone marrow, then they have already differentiated down to a specific activity, and they have a limited capability. Progenitor cells, for example, are produced by a person up until about age twenty-five, and then after that natural repair mechanisms of the body start to decline. So I think the wish by some that adult stem cells are panacea is misleading; it's really a narrow set that has a narrow set of applications. So would be the case of cord-blood stem cells—it's a source applicable to a few disease applications. We're talking about dozens of diseases that need to be gone after, and embryonic has the advantage in that we eventually, through research, believe we'll be able to differentiate them into all types cells.

Kiley: If your wife was about to give birth, would you advise her to store her cord blood?

Byers: Well, I would because I believe in science and I believe in development, and I think that's going to become applicable. That would be, you know, something to do: it's not going to be a panacea for everything, but might be useful.

Kiley: Do you think we'll ever see such a thing as a universal donor cell? That is, one that can be taken without reference to its origin in a system that your body would recognize as other than self?

Byers: I don't know. We would want it recognized as self, by the way, to avoid transplant rejection.

Kiley: Reverting to Proposition 71, currently the California legislature is seemingly having second thoughts. I attribute that to its recognition that there is a lot of money here, some of which might not be spent in the districts of individual members, and they are seeking to gain greater control over the funds made available by the citizenry. What is your view?

Byers: Well, what I've observed is a bit different than what you just described. I'm sure to some elected legislators three billion dollars is an enticing number, and they felt as though the initiative process took it out of their hands to go through all this. The initiative, as I understand the way it was written, was specifically written so that it would be protected from changes and the blowing winds of politics one way or the other, and so it was done as a constitutional amendment in California. There had been some proposals recently for constitutional amendments to be put on the ballot to change it. I'm going to assume there was good intention by the proposers, that what they were worried about was conflict

of interest on the part of people on the governing board, and a desire for an open process and fair review of proposals and so on. But, from what I've read of the proposals so far and what I know about how the science system works in the United States, I think there's a misunderstanding about protection of intellectual property—the fact that it's not possible to price a therapeutic ten years in advance; it's not possible to put a royalty rate on intellectual property five or ten years in advance. People who are proposing this have not asked experts who have done this for their entire careers how to make this work well. Now, I'm hopeful that compromises will be found, dialogue will happen, negotiations will go about, and we'll end up with, something where we can go forward. The shame of all of this, plus the lawsuits that have been filed by people that oppose all of this, is that it is holding it all up. And the will of the voters—fifty-nine percent of voters approved Prop. 71—is not happening. That is, there's been no funding of anything so far, six months after the election. And we have a philanthropic donor who has given five million dollars to the stem cell Center for Regenerative Medicine, just so that it can at least open an office and operate. It's a real shame. These lawsuits are holding R&D on cures.

Kiley: Referring to Mr. Bowes?

Byers: No, Ray Dolby.

Kiley: Oh, Dolby, I'm sorry.

I must say I share your optimism concerning the process; at the same time, as a California taxpayer, I wonder whether California isn't being asked to pay a disproportionate share of the nation's investment in an important area of medicine. And I find it difficult to be confident that the state will economically benefit in proportion to the contribution it makes, given the fugitive nature of intellectual property and the tendency of smaller companies on the West Coast to collaborate with larger companies on the East Coast once products approach market.

Byers: All good points. As Tom Friedman points out in his recent book, *The World is Flat*, technology travels all over the world. And so I think that you can approach this in several different ways. One would be the California parochial way, which is to say why should we taxpayers pay for all this research when it's going to benefit the whole world? Well, one reason to do it is because we can. We have the science capability here, we are a very wealthy state, there's a lot of wealth here. Regardless of the current state of the California budget, money can be found; money is spent on a lot of things. So I think we can do this, and I think I have to applaud the California voters for looking beyond their own pocketbooks and saying we believe this is the right thing to do. Californians also benefit from things that happen somewhere else, and this is more going to be the case as information travels on the internet, as people travel physically, as the world becomes virtually smaller and smaller—

Kiley: Or flatter and flatter.

Byers: Exactly. And as I say, it's a shame it had to happen. I think eventually there will be a change in policy at the federal level and the NIH funding for stem cell research will go up. I'm watching other states now inspired and challenged to start stem cell programs, as we see at New Jersey, Massachusetts, Wisconsin. I'm happy about that. I'm glad this is stimulating all this activity, and when I'm visited by scientists from China, and government officials, they just shake their heads in disbelief at our country's policies, and they just say, "Well, we are going to go after it too." So I think in the long run it will all even out.

Kiley: May I ask whether your interest in stem cells is motivated by anything more than altruism? For example, is this an area in which you and your partners foresee opportunities for investment, for new company start-ups and so on, and are you able to say whether any of that is going on at present? Having in mind, that I'm a director of an embryonic stem cell company [chuckles].

Byers: Yes, you are, of Geron, which was the pioneer in this area beginning over a decade ago. So right now we have no involvement at Kleiner, Perkins, Caufield and Byers in any stem cell companies. And the decisions I've made to support all of this up to this point have been altruistic, just as I've stated here. I see a role as enablers and developers of technology when it's ready, when the time is right. When that's going to happen with stem cells, I don't know—three years, five years, seven years from now. I don't know enough yet; I think it's, as I say, early days. I would like to be part of the solution; I think we are good at starting companies to do breakthrough science. So if the time comes along in the near future where there's a good company to be started, or already started where we could pitch in and help, to take research developed in a research institute or university and develop it into real products that are going to go benefit humans—and that has to be done in the private sector—yes, I'd like to be involved. We have enough confidence here to think we could make a difference and even have it happen sooner rather than later, so we'd like to be involved in that.

Kiley: Well, certainly recombinant DNA was controversial when Kleiner Perkins financed Genentech, now thirty years ago. Evidently, you thought recombinant DNA was ready at that time; some might regard that as optimistic. Now are you more conservative? Is it that you think the science is not ready, or the government is not ready, or the medical community is not ready? What is it that's not ready?

Byers: I think we know more now. When we seed-funded Genentech, it was an entirely new industry, and we had no benchmarks, no experience, no wisdom to judge the pace of how that would develop. I think we've been through so many technology revolutions here that I'm applying that. Perhaps I'm being conservative. The systems of surveillance, of looking at science around the

world and understanding what's going on and when it's about to happen, is so good now, with Google, and internet, and communications, that when something happens, we'll know it that week and can take action the next week. So there's not so much a sense of kind of a vague confusion and, "Well, let's just start so that we don't get left behind." I think that's part of it. You, Tom, joined Genentech very early as well, when there was huge technical risk and uncertainty, and there was no clear view what products would come out of it in what way and what applications in human health or agriculture or industrial processes and so on. So I think this is going to happen. It's not a matter of if, but it's when. I'm hearing drum beats about stem cell applications. I think it took Proposition 71 to inspire scientists to say, "Okay, this is an area worth spending my career in, or turning my lab to." And so we're only now just starting to hear the eurekas.

Kiley: I would say to be fair that among the first money that went into Geron was Kleiner Perkins' money, albeit at a time when the company had a different objective. I will share my view that if there is anything in embryonic stem cells, there is room for an awful lot of companies, and I don't believe that Kleiner Perkins will be short of opportunity to invest in a plethora of companies as the science moves forward.

[interruption]

Brook, it's now some three decades since the life science juggernaut began to roll. You've been involved in it nearly all that time. I happen to believe that we are doing things now that could not have been predicted thirty years hence. But you're a lot smarter now than we all were thirty years ago, so may I ask you where you think biotechnology is going to have taken us thirty years from now?

Byers: [pause] Well, if we placed ourself back three decades ago into the mid-seventies and were asked this question, I don't think that we would have even speculated the list of things that we can do now. So it's been a remarkable ride, and I think patients, doctors, humanity should count themselves to be very lucky to be at the state of development we're in. You know, it's probably the way people feel who were aware of the state of medicine in the thirties and forties, and then they wake up in the seventies and say, "All right, now we have antibiotics and we don't have polio." Huge changes. So three decades, thirty years, is a good measurement time. So I'm going to accept your challenge and think out to the year 2035, and what will it be like to be a patient.

So at that point bear in mind that we'll all be carrying around a handheld device that will allow us to access all knowledge in the world—either information stored on that device or it will be an internet-ready- access device that will allow us to go onto Google, and whatever that evolves to and things like it, to all the databases in the world, so we'll have that information access. And it can all be encrypted, so that your personal medical record will be with you at all times.

Now, your personal medical record will have transformed greatly from what we think about today. In 2035, you will probably have had your genome sequenced, and that will not be on a CD-ROM, because we won't be carrying those around; they'll be in hardwired memory or accessible. You will have had it sequenced to find polymorphisms or unique characteristics, good and bad, of what you have, and then you will have been assisted in changing your behavior to get around some of the weaknesses that you inherited in your genome. So you might be encouraged to do things more than just eat sensibly, get sleep, exercise, and don't smoke. You will follow a more specific diet, and you'll probably have a doctor who's more trained to give you preventative advice than rescue medicine. And the technology to do that very low-cost sequencing will have been developed a decade or two before, and so the cost of doing that and the time will be a matter of an hour per patient and probably a couple hundred dollars to sequence that person's genome. You will do more of your own self-diagnostics and therapy choices, because there will be computer systems in evidence-based medicine that will show what you should do. There will be more products available to you. You'll be a better educated patient.

The pharmaceutical industry, in my prediction, will have deconvoluted into smaller firms that have more efficient R&D. Their target markets for a drug will be measured in the hundreds of millions of dollars, rather than multiple billions as required. Therefore, they'll embrace stratified clinical trials, and they will select sets of patients based on their predicted response rates or applicable disease categories. Therefore, drugs will have a very specific and targeted kind of label put on them, and so the FDA will have better statistics to look at. There will be much more post-approval surveillance monitoring, but that will all be done real-time of course, too. The patient could input their adverse reactions on their handheld [device] to their doctor; the doctor simply scans it for authenticity and sends it forward to the FDA.

So I'm an optimist, and I think all of this that I just listed is quite possible, maybe even sooner, and it requires good leadership, smart leadership of companies, of course, but even more so at the government level, in each country and in the worldwide community. And so I'm hopeful by that time that we'll have more people with a medical and a scientific background in positions of leadership of countries so that they can handle the rate at which this change is coming. The world of science and pharmaceuticals will continue to expand worldwide, not just China and India, but other countries all around the world will participate in developing new drugs. Intellectual property will have changed what it is as defined. I'm hopeful that the world will have a consistent intellectual property framework, not just as a bargaining tool to get into the World Trade Organization. The U.S. healthcare system will have a different paying system and reimbursement system. It will probably by then have gone to a single-payer system. For sense of fairness and coverage, all adults and children will have health care insurance, as opposed to today where forty-five million Americans don't have any health care insurance. I would like to make the

prediction that in 2035 doctors, people who go into that profession, will be seen as angels of mercy and will be given special benefits, such as not having to pay income taxes or something like that, so that we don't have what we have today which is the cynicism on the part of doctors about did they choose the right profession, and people will go into it for all the right reasons that motivate them today. So net-net, I think that we'll see life spans continue to elongate. There is a natural in-life span to humans, and I think that is something to have a reverence for. I think it's a natural cycle of nature that there is death, and that allows renewal and the new. But I think death in an ideal world, and I'm hopeful that we get there in thirty years, is that for each individual person all systems go at the same time rather than a slow degradation and degeneration.

Kiley: Well, that is very stirring, Brook, and I must say I share your expectations and hopes. I wonder if finally you will say how you expect medical devices to mature over the next thirty years. Is it possible that with the advent of friendly pharmaceuticals and better preventive care we'll need less on the device side, using that term in the old medical sense? Or will we become more biotic as advances in miniaturization and nanotechnology move forward?

Byers: Oh, I think it will all become integrated, so a drug taken as a pill may be just one of many methods of delivery. I would think that nanobiology will have developed to that point where implantation of a system that senses the need and meters out and titrates the right amount of drug at that time will have happened. And that will be in all parts of the body, including the brain.

Kiley: Brook, let me say that in view of the contributions that you and your partners have made to medical technology and the state of health of Americans at large over many years, that you might regard yourself as an angel of mercy as well. And let me say on behalf of the Bancroft Library that I'm very grateful for the time you've made available to tell a very, very interesting story, and one that I think readers will find very important, both now and in the future as they look back on the birth of biotechnology.

Byers: Thank you, Tom. Comments like those from an expert, biotech veteran such as you are so motivational for my partners and me to "keep on keeping on" with these challenging and long-term projects and companies.

Kiley: Thank you.

[End Tape 6, Side B]
[End Interview 3]

Appendix—Brook Byers Curriculum Vitae

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Brook Byers has been a venture capital investor since 1972. He has been personally involved in building more than sixty new science based ventures, many of which have already become public companies. He formed the first Life Sciences practice group in the venture capital profession in 1984 and led KPCB to become a premier venture capital firm in the medical, healthcare, and biotechnology sectors. KPCB has invested in and helped build over 110 Life Sciences companies which are developing hundreds of products to treat major underserved medical needs representing huge markets in the nearly two trillion dollar healthcare sector.

Brook was the founding President and then Chairman of four biotechnology companies which were incubated in KPCB's offices and went on to become public companies with an aggregate market value over \$8 Billion. He is currently on the Board of Directors of eight companies, most recently joining CardioDX, Genomic Health Incorporated, Five Prime Therapeutics, OptiMedica, Pacific Biosciences, Inc., Spinal Modulation and XDx, Inc. He was formerly a Director of Idec Pharmaceuticals (Chairman), Onyx Pharmaceuticals, Athena Neurosciences (Chairman), Signal Pharmaceuticals, Arris Pharmaceuticals, Pharmacopeia, Ligand Pharmaceuticals (Chairman), Hybritech (Chairman), Genprobe, Nanogen, and others. These companies have pioneered the medical uses of molecular biology, monoclonal antibodies, molecular diagnostics and genomics.

Brook was President and a Director of the Western Association of Venture Capitalists. He is a Board member of the University of California at San Francisco Medical Foundation, the California Healthcare Institute, the New Schools Foundation, Stanford's Bio-X Advisory Council, the Stanford Eye Council and TechNet. He is Co-Chair of the five year, \$1.4 billion, UCSF Capital Campaign. He was formerly a Director of the Entrepreneurs Foundation, the Asian Art Museum in San Francisco, the Stanford Graduate School of Business Advisory Council, That Man May See (UCSF) Vision Research Foundation (Chairman) and the Georgia Tech Advisory Board. Raised in Atlanta, Georgia, Brook graduated in Electrical Engineering from Georgia Tech and received an MBA from Stanford.

SALLY SMITH HUGHES

Sally Smith Hughes is a historian of science at ROHO whose research focuses on the recent history of bioscience. She began work in oral history at the Bancroft Library in 1978 and joined ROHO in 1980. She has conducted interviews for over 100 oral histories, whose subjects range from the AIDS epidemic to medical physics. Her focus for the past decade has been on the biotechnology industry in northern California. She is the author of *The Virus: A History of the Concept* and an article in *Isis*, the journal of the History of Science Society, on the commercialization of molecular biology.