Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Program in Bioscience and Biotechnology Studies

David W. Martin, Jr., M.D.
UCSF PROFESSOR, GENENTECH VICE PRESIDENT OF RESEARCH, AND BEYOND

Interviews Conducted by
Sally Smith Hughes, Ph.D.
2004

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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It is recommended that this oral history be cited as follows:

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My family at our home in Mill Valley, 2004
Kathy Martin, Gilliam Martin Mishalko, Lilli Mishalko, Cliff Mishalko, David W. Martin,
David McKinnon Martin, and Henry
photo courtesy of David Martin

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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

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
November 2005

January 2006

ORAL HISTORIES ON BIOTECHNOLOGY

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

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

Oral histories in process:

Brook Byers
Ronald Cape
Stanley N. Cohen
Donald Glaser
James Gower
William Green
Keiichi Itakura
Irving Johnson
Daniel E. Koshland, Jr.
Arthur Levinson
Arthur Riggs
Stephen Rosenberg
William J. Rutter, volume II
Mickey Urdea
Pablo Valenzuela
Keith R. Yamamoto
William D. Young

INTERVIEW HISTORY—David W. Martin, Jr.

David Martin was a prominent member of the second generation of Genentech scientists. He arrived in 1983, seven years after the company's formation, to assume the title of Vice President of research. Unlike most members of the first wave of Genentech scientists, he came from a well-established academic career, a full professorship in the departments of medicine and biochemistry at UCSF, and with an impressive list of publications, all of which he discusses in this oral history. Why then was he attracted to a job in industry, at the time considered less prestigious than a university position? Martin provides an answer in this history, one of the thirty-five on commercial biotechnology recorded to date for ROHO's Program in Bioscience and Biotechnology Studies. He tells us that he had three considerations, common to academics of the early 1980s considering employment in the nascent biotechnology industry: would the research be basic enough to interest a university scientist? Would he be tainted by the contemporary stigma in academia concerning scientists in industry, and could he return to academia if he so desired? Bob Swanson, Genentech's CEO, assuaged his fears in all three regards. Yes, he could have release time for his own research; yes, he was joining a company recognized by academics for its sterling record in cloning genes of medical importance; and yes, after three years, Martin could decide to return to academia. Underlying all this was the thrill and challenge of applying recombinant DNA in the production of phamaceuticals. So Martin came on a wave of high expectations only to rise and fall and rise again with the multiple problems of managing a group of accomplished and singularly independent scientists. Martin describes the spects of his position: reporting lines, intellectual property considerations, corporate culture, the interplay of research targets and financial constraints, the mistakes he made in handling complicated science projects and competitive personalities, and more.

But Martin's story does not end with Genentech. He briefly describes subsequent positions at DuPont Merck and Chiron Corporation and also his hand in founding a series of companies—Lynx Therapeutics, Eos, and GangaGen. Underlining the impermanence of positions in biotechnology, Martin who was chairman and CEO of GangaGen when we interviewed in 2004, has since left and founded another company, Abbott Antibiotics.

Three interviews were conducted at GangaGen in a building on a pier at San Francisco's Embarcadero. Martin was forthcoming in his responses and in the transcript review process edited carefully for clarity and accuracy. By agreement with Genentech regarding the oral histories it supports, its legal department received transcripts of all interviews to review solely for current legal issues. As in all instances to date, no changes were requested.

The Regional Oral History Office was established in 1954 to record the lives of persons who have contributed significantly to the history of California and the West. A major focus of the office since its inception has been university history. The series list of completed oral histories documenting the history of the University of California is included in this volume. The Regional Oral History Office is a division of The Bancroft Library and is under the direction of Richard Cándida Smith.

Sally Smith Hughes, Ph.D.
Historian of Science
Program in Bioscience and Biotechnology Studies
Regional Oral History Office
The Bancroft Library
University of California, Berkeley
August 2005

INTERVIEW 1: January 26, 2004
[Tape 1, Side A]

Hughes: —way back, Dr. Martin, with your—

Martin: David.

Hughes: David. Right, David—with your family background and education. If you could start off by telling me, actually, a little bit about your grandparents.

Martin: My mother was born in Austin, where my maternal grandfather was a professor of English at the University of Texas, having migrated from South Carolina. Both his and my grandmother's families were from South Carolina. Theirs were two old families in that area, one of them Manigault, one of them Law. The Manigault were Huguenots that had immigrated to this country before the French Revolution and subsequently supported the French Revolution, based on their rice plantations in South Carolina. The Law family had come from Scotland, not quite so early as the Manigault's. So my grandparents went to Texas after he was educated at Princeton and Harvard, and then as a very young man in his late twenties became chairman of the English department at the University of Texas, when it was a fledgling university. My mother grew up there and then went to Duke in a x-ray technician's training program, met my father, who was a intern. They were married, and while he did a pediatric residency, she finished her program. They moved to Florida his family he had moved when he was twelve. His father had been a banker in West Palm Beach, and my father had attended high school there. So they moved back to West Palm Beach, and I was born not long after awards. So I grew up in West Palm Beach and Palm Beach.

Hughes: What was that like?

Martin: Only in retrospect, it was a cultural desert. The only industry was the tourist industry. That was very seasonal, about three months out of the year at that time, from January 15 to March or April. The tourists, in general, had their cultural interests somewhere in the Northeast and they were supporting them there, but not trying to duplicate them in Florida. There were not many cultural activities at that time. They came down to play golf and play tennis and go to the beach. It wasn't until I left there and went to Boston to college that I realized that there was a lot in life above and beyond playing golf, tennis, and fishing. I have not spent a lot of time in Florida since. Both of my parents are dead. [tape interruption] I didn't go back. I would go and visit; that was it. After I finished my medical school training my father tried to convince me to come back and practice medicine in West Palm Beach. I didn't have any interest. I was more interested in academics by then than the practice of medicine.

Hughes: Did you grow up doing all those sports and fishing?

Martin: I grew up fishing, mostly. I played golf from a young age because my father played golf. I was more interested in fishing than golf, so I spent a lot of time fishing as a source of spending money, and even for the first year or so in college, by fishing during the summertimes generated enough money to pay my expenses—not my tuition, but

pay my expenses during the year. I was working on a sports fishing boat through the Bahamas in the summertime. So it was fun. Kept me off the street and out of trouble.

Hughes: Did you go to public schools?

Martin: I went to public school all the way through high school in West Palm Beach and enjoyed that; I'm strong proponent of public schools. I managed to get into MIT [Massachusetts Institute of Technology], so I had fairly good grades. At MIT I discovered, at least at the fraternity house in which I lived, my classmates that had the most academic difficulty were those that had been to private schools rather than public schools. They had just not been accustomed to the multiple pressures—the social pressures, the academic pressures along with everything else. They were apparently protected by private schools. They likely had a better education, but they were not so capable as dealing with the stress of studies. I think in retrospect it was a good decision for me to attend public schools. My parents had asked me a couple of times whether I was interested in going to private school, and I resisted it modestly; they never pushed, so I stayed in public school. My father went to the same high school. In fact, we were both presidents of our senior classes in the same high school.

Hughes: That's interesting. Do you have brothers and sisters?

Martin: I have a sister who lives in Tallahassee, who has a Masters degree in special education. She went to Duke undergraduate and Columbia graduate school. I went to Duke Medical School, so we overlapped for a couple of years at Duke when she was an undergraduate. I had a brother who had a disease called Lesch-Nyhan disease, which was an X-linked CNS [X chromosome-linked central nervous system] disorder. He died in his twenties. He had severe cerebral palsy. I'm sure that had something to do with my going into medicine and research, and my sister pursuing special education for developmentally disabled children.

Hughes: I was going to ask you that. It was more that than the fact that your father was a physician? A combination?

Martin: It was a combination.

Hughes: Why then MIT?

Martin: Because I decided I did not want to be a physician. It was a mild form of rebellion. I was very interested in math and physics, and a man for whom I worked on his sports fishing boat—I worked as a first mate—was an MIT graduate. Unknown to me, he also knew my father socially. He convinced me that MIT was such a unique place, and that I should apply to MIT. With his influence, I rebelled, went to MIT. After the first year, I decided that I didn't want to be associated with all the geeks—they were called "nerds" then— so I changed my major from physics to biology and decided I was going to go to medical school. I didn't tell my father.

Hughes: That is rebellious.

Martin: I think in a way he was frustrated not being an academic. He was always interested in chemistry and biochemistry but yet practicing as a pediatrician. I can remember his

telling me when I was probably eleven or twelve that the brain function was all chemistry. He had that insight and interest, so we used to talk about that. I would make house calls with him. I went into the operating room a number of times with him. Although he was not a surgeon, he was an accompanying pediatrician for either C[caesarian]-sections or pediatric surgery. So I got to see some of both, which were obviously interesting. That was a strong influence of his on my decision.

Hughes: And what about your mother?

Martin: My mother stayed home, did not work, except to fill in for an x-ray technician every time he took a vacation from work in a group that my father had formed in a large multidisciplinary clinic. She took care of my sister and me and of my brother for several years. He was about seven when my parents placed him in a home for "crippled children" in Atlanta. She did not go back to work afterwards even though I can remember encouraging her to do so.

Hughes: She was from the medical world too, in a way, so you had two parents who understood. How traumatic was it to have a child that now was institutionalized?

Martin: It was more traumatic, I think, at the point that I learned my parents were going to put him in the home—that event, I remember very vividly—than growing up with it; it seemed pretty natural growing up with it. Children adapt quite well. He was handicapped enough so he couldn't talk, couldn't walk or crawl. He understood much about his surroundings and was very capable of expressing emotion. He would laugh and have fun so one could interact with him, but not really play with him as a sibling. He was in a wheelchair or what have you most of the time, so my sister and I would wheel him around and take him places. He was in a program for crippled children in Palm Beach. Palm Beach had a good program at that time. This is back in the late forties, the early fifties. So I used to go there with my mother to pick him up or take him, so I was seeing a lot of handicapped children and became fairly comfortable with it. Interestingly, my wife, who is a twin, has a retarded twin sister who suffered a birth injury, for whom she is now her conservator.

Hughes: The decision maker. I forget the term, too.

Martin: We see a lot of her sister Arleen. She's here in the Bay Area. That was something that both Kathy, my wife, and I understood quite well. We were brought up in families with retarded sibs.

Hughes: In some families when there is a child that's disabled, the parents focus on that child. It doesn't sound as though that was entirely the case in your family, given that you told me about conversations with your father.

Martin: I think that's true. I suspect that one of the reasons they sent him off was to make sure that didn't happen. The other was that it was a real physical burden to manage him even though he never grew to full adult size. My parents apparently felt he wasn't getting the physical therapy, occupational therapy, et cetera he needed. At that time it was less common for parents with a retarded child to keep them in the home and make appropriate arrangements to deal with it. Whether their decision was the right thing to do or not, I don't know. Those are very difficult, very personal decisions.

Hughes: Yes, they are.

How was biology at MIT? I think most of us who don't have insider's knowledge of MIT think of it more as an engineering school and the physical sciences.

Martin: Well, biology at MIT now is extraordinarily strong and has been for the last twenty years, but this is forty years ago we're talking about. There was a small biology department and two of the assistant professors at the time are people who have become very prominent in biology. One was Alex Rich, who is still at MIT. I don't think he's retired yet. I see him occasionally because a subsequent mentor of mine was a good friend of his. Alex visits my mentor's widow here in San Francisco periodically. Alex was a very smart man and a good teacher. Then there was a man by the name of Ed Herbert who has since died. He left MIT a few years later and moved to Oregon, where he built a very good program at the University of Oregon in Portland. There were people like Jim Darnell, who was a graduate student. I remember his teaching a biology lab, et cetera. Several other people I still know from that contact in the fledgling years of biology at MIT. It was a rigorous program and that was sort of the beginning of molecular biology. So I started there—I was a freshman in '58.

Hughes: There were courses in molecular biology?

Martin: Oh, yes, even though it was not labeled as such. There were labs. No one was cloning anything at that point. We didn't know what that was, but there was a lot of focus on—the molecular function of hemoglobin or myogloblin as a molecule. People were really paying attention to molecules and genetics. There was an interest in genetics and it was not very long after that that the bacteriophage genetics became very prominent at MIT. People like Ethan Singer began to build programs there. So it's interesting, quite independently of my being an undergraduate at MIT, I ended up having a lot of interactions with MIT scientists. People in the Whitehead [Institute], et cetera. David Baltimore was not there when I was there. He came a few years later.

Hughes: Was that unusual for an undergraduate at MIT? I would think it would be very unusual elsewhere.

Martin: To be in biology?

Hughes: Well, to have so much interaction with the faculty.

Martin: This was afterwards. After I left, biology became so prominent. There were so many good people there that I continued to interact with them quite a bit. I still do.

Hughes: I see. I thought you were talking about your undergraduate years still. What about the Harvard influence?

Martin: There was almost no Harvard influence at MIT at that point. The joint program [Harvard-MIT Division of Health Sciences and Technology] didn't exist. At the time I was there, I think that one could apply for taking courses at Harvard, perhaps in the humanities courses, but there was not the exchange that there is currently. Currently, I think any Harvard or MIT student can cross-register at the universities and there are combined programs—MD/PhD programs that are combined, as I understand it. Harvard

was a "competitor" to MIT. There were always practical jokes being played on Harvard and vice versa.

Hughes: Did you enter the biology program with an interest in molecular biology, or did that come—?

Martin: I didn't know what molecular biology was. I entered the biology program with the intent of doing pre-med. I finished my pre-med in two years and applied to medical school and got in. So I was only at MIT for two years before I went to medical school.

Hughes: How did you accelerate so quickly?

Martin: I just took a lot of courses.

Hughes: Yeah, I would think.

Martin: And the requirements were such that it was possible to do it in two years at MIT, so I did.

Hughes: Were you unusual in doing that?

Martin: I was unusual in going to medical school after two years, but I had classmates that went after three. Quite a few.

Hughes: Because across the country I think it's a bit unusual. Most people have four years of undergraduate work.

Martin: Sure. I applied to Harvard and Duke. My father had gone to Duke, so of course I applied to Duke after two years. Harvard told me they would accept me if I had another year, which was probably a wise thing for them to do. Duke asked me to be interviewed, and so I went down and was interviewed. The dean of the medical school interviewed me. I knew him through my father, who had trained as a pediatrician under him. However, my father did not know I was applying to med school. The dean was very supportive and said, "Well, look. I think that you're better off cutting two years off of undergraduate but add two years on postgraduate and go do something really interesting that you might otherwise be in too big of a hurry to do after getting your MD." In effect, I did that. I did a residency and then spent three years at NIH [National Institutes of Health] as a postdoc to really learn basic science. I think that was good advice from one perspective. On the other hand, my education certainly was abbreviated. Not my science or medical education, but my humanities, knowledge of literature and liberal arts was certainly truncated. That's hard to make up for afterwards, just because of time constraints of being busy and having a full-time job.

Hughes: You spoke of the contrast in the cultural context compared to West Palm Beach. Were you too busy to take much advantage of what was going on in Boston?

Martin: I tried. I certainly tried. As a student, one's very busy. I took an interest in classical music, which I'd listened to but had never seen performed before, an interest in jazz. That was about all I had time for. I didn't get involved in theatre when I was there. It

was all an eye-opener for me. I went to a few real baseball games. Ted Williams was still playing, so it was exciting.

Hughes: Are you a baseball fan?

Martin: No, I'm not.

Hughes: What was Duke Medical School like in the—early sixties, is that right?

Martin: Started in '60. About half of my class, was populated by Duke undergraduates, which was unusual. It was a bit incestuous that way. Durham was another cultural desert about the same as West Palm Beach except it had a university. Because of the university, there was theater art and music. I had learned to study at MIT. I learned how to study a topic, and so medical school ended up being fairly easy for me, easier than undergraduate at MIT in terms of how hard it was to drink from the fire hose. While it was long hours, particularly in the last two years of medical school—the clinical years—the first two years were relatively easy and I had good grades, ended up first in my class, et cetera. I was fortunate to have a pretty good brain but more importantly, I had learned at MIT how to approach a topic. I could watch my classmates' struggle, not because they weren't as smart. They were plenty smart, but it was because they didn't know how to approach it. They didn't know how to approach, for instance, biochemistry. They were in there trying to memorize everything. I said, "No, no, no! Don't do that. Just understand this piece and this piece and then you can make up what goes in between, as long as you understand a little bit of chemistry."

Hughes: They were used to rote memory.

Martin: Yes.

Hughes: The heavy population of Duke undergraduates, was that policy or was it something to do with Duke Medical School's reputation at that point?

Martin: I don't know, because the other thing that was equally incestuous was the internship in medicine, which I took at Duke. I stayed at Duke and did an internship and residency. That was heavily populated by Duke medical school graduates. There seemed to be a pattern anyway, whether it was a policy of accepting a lot of Duke undergraduates and a lot of Duke medical school grads into an internship. I suppose it was easier in many ways for Duke to do that. They weren't taking any risk, because they had thorough records and knew these students. But I think it really did compromise a bit the quality of the medical school class, at least in terms of the diversity. Not in terms of intelligence, but just diversity of experience.

Hughes: Because Duke didn't have the reputation then that it has now, where it's right up there.

Martin: It's in the top five U.S. medical schools, right. But it was a good experience for me. Would I do it again, I don't know. I would probably go back, because one of the things I did during medical school was to take in the Research Training Program a year off of medical school, and yet I still graduated on time. That was a program that Jim Wyngaarden had established.

Hughes: Oh, I see. So that actually was a year off to do just that. I mean, you dropped out of the coursework.

Martin: I dropped out of all the coursework and took instead coursework in the Research Training Program [RTP], which was a specific program of both didactic exposure and then lab training. That was for nine months, and then one had to catch up to graduate with your class, which meant that you had to go summers, which normally medical students didn't do. I had to forfeit an elective, which I didn't take. I guess the other thing was if one was going to go into internal medicine, then the program allowed you to skip one of your two rotations in medicine. You could skip one because they felt that by the first month or so of your internship, you had already made it up. I skipped those two rotations and then there was another third quarter that one were supposed to go to during the summer and I talked them into letting me skip going to school that summer so I could fish. I did, and worked for a summer and then graduated three months later than my class. I managed to get what in effect was an internship in pediatrics in Halifax, Nova Scotia for that last three months. I went up to Halifax in July for three months as my pediatric rotation. I had a very good time there, primarily because of the chairman of pediatrics at Dalhouse with whom I've since become friends as did my parents. I think he, Bill Cochrane, saw that I'd had better training than most of his medical students at the Dalhouse University and thus he gave me more responsibilities than most of their interns. I was treated like a resident even though I was a medical student. That was wonderful, because I got to teach. I just had more influence on my patients and the wards than did the interns who were effectively fifth-year medical students.

Hughes: And you were young to begin with, having spent only two years at MIT.

Martin: I was twenty-three.

Hughes: My heavens.

Martin: I graduated when I was twenty-three.

Hughes: Did that sit all right with your classmates, your peers?

Martin: They didn't know. There's enough immaturity among medical students that my real immaturity didn't stand out so badly.

Hughes: Let's go back to Wyngaarden. Was this a program that was throughout the department of medicine, or was it only in his lab?

Martin: It was a medical school program.

Hughes: Oh, it was the whole school. But he had been the instigator?

Martin: He was the instigator. He had applied for a National Science Foundation grant to start this program and it was really the precursor of the MD/PhD or the MST [Medical Scientist Training] Program that NSF ultimately sponsored. I think he ran it for about—10 or 15 years and then it ended up being displaced by the MSTP. So he had started it, pulled together with the grant a series of faculty members, had most of a building

assigned to. The faculty was a good basic science faculty. He was one of the few physicians who was on that faculty of the RTP. The rest of them were strong basic scientists. It was primarily to teach basic science to medical students and postgraduate medical students, so it was a program that would accommodate sixteen students, eight of whom were medical students who had arranged to get this extra year by finagling courses, and the other were either fellows or third-year resident in some specialty. They simply did it as one of their elective years in their residency program. That was a nice mix, because we were thrown together as peers. I participated during my junior year, and there were some seniors who were doing it. There were fellows who were four or five years beyond where I was doing, so it was a nice mixture of getting to know more senior physician-scientists and the faculty as well. Those faculty relationships were very close because there were only sixteen students and there were probably eight or ten faculty members. We got to work in their labs and such.

Hughes: Tell me what Wyngaarden is like, as a personality.

Martin: He was referred to as "Gentleman Jim." Quite suave, good-looking, Dutch ancestry. Very charismatic, a good physician, good scientist.

[Tape 1 side B]

Martin: He left Duke, where he was a professor, shortly after I graduated, and went to Penn [University of Pennsylvania] as chairman of medicine there. Then he came back to Duke as chairman of medicine a few years later, after I was gone. Then he became the director of NIH a few years after that, and then was Foreign Secretary for the National Academy of Sciences, and so forth. He's had a very prominent career. He's still active. I haven't seen him in a couple of years, but I do see him periodically in San Francisco for meetings. I've skied with him at various meetings. He certainly is an interesting man. Still very active; I'm not sure how old he is. He's in his late seventies now, but back in Durham apparently.

Hughes: Is that so? I didn't realize that. And you did research?

Martin: I did research. It was interesting; he had built his career working in purine metabolism, which was one of the components of DNA, one of the two type of bases. He studied purine de novo synthetic pathways and enzymology. I worked in his lab and learned something about purine metabolism, although I worked on a somewhat different project, trying to isolate messenger RNA. This was in 1961, '62, which was pretty early. There were some techniques we were trying, to isolate polycistronic messenger RNA. It was sort of a new field for Jim, but he was very supportive of it.

After I graduated and finished a residency, he got me a position at NIH to wear a yellow beret, that is, to stay out of Vietnam. What was ironic was that I knew a fair amount about purine metabolism by osmosis from working at his lab. When I went to NIH, a good friend of mine there, Bill Kelley, had been at NIH a year before me. He and I had grown up together in West Palm Beach. Both of our fathers were physicians, and Bill and I used to fish and swim together. He had married a former girlfriend of mine from high school, so we all knew each other. Shortly after Kathy and I—I was married right

after I finished medical school—moved to NIH, in Bethesda, we had dinner with Bill and Lois. I asked him what he was doing, so he proceeded to tell me.

He, Fred Rosenblum and Jay Seegmiller, in whose lab Bill was working then as a postdoc, had discovered the biochemical defect in the Lesch-Nyhan syndrome. He began to tell me about this syndrome. I realized that he was describing what my brother had, who had not been diagnosed. He was thought to have post-encephalitic cerebral palsy. It had been called that for years and my mother had a huge guilt complex about it. She felt that her failing to have immediately treated a monilia vaginitis when she was pregnant had led to his encephalitis. After Bill told me about this syndrome, I called my father and asked him to send me a blood specimen from my brother. He managed to send it, and I took it to Bill. I asked him to assay it for HGTRPase [hypoxanthine guanine phosphoribosyl transferase], the deficient enzyme. He asked me where I got it, and I said, "Would you tell me whether it's positive or negative first, then I'll tell you where I got it." So he called me back a few days later—it was a several-day assay—and then said, "Okay, that one's deficient. Where did you find that patient?" So I told him. The Lesch-Nyhan syndrome is a deficiency of one specific enzyme in purine metabolism. I already knew about purine metabolism from Wyngaarden's lab experience and his expertise. I ended up subsequently working in the field myself, not so much on the Lesch-Nyhan syndrome but on purine metabolism. When I moved out here to San Francisco, I focused on purine metabolism because I knew something about it and I felt that there were some real opportunities there that had not been exploited with the molecular techniques versus the biochemistry approach from when I was a medical student. To me, it has been an amazing coincidence that I worked as a student in a lab of purine metabolism, end up with a brother with Lesch-Nyhan syndrome, a friend of mine discovered the defect of it, and I ended up working in the field myself.

Hughes: Amazing. What were you thinking now at this stage about the balance—or not—between the practice of medicine, the clinical aspects of it, and the basic science, which you seem to be getting your feet in.

Martin: When I was in the RTP I was having a very good time and learning a lot of basic science. I was very excited about that aspect, which had been in many ways a continuity of my experience at MIT where things were just very tough basic science rather than the clinical medicine that I had learned in medical school. I told Jim late in that year when I was working in his lab that I wanted to pursue a Ph.D. rather than an M.D. I wanted to just enroll in graduate school. I had already been taking graduate courses. He said, "I won't let you do it. I'll absolutely stymie you there. You have to get your M.D. first, then you can go pursue a Ph.D. I won't let you deviate from that, because it will be so much more valuable to you if you have an M.D. without a Ph.D. than vice versa. You may only get one, so you've got to focus on the one that will give you the greatest number of opportunities in a career." I did.

Hughes: And was that good advice?

Martin: Absolutely. I've since given so many people that same advice. It's really true that if you have an MD and the science education, you can do most anything you want. If you have the PhD with the science education but you don't have the MD, the physicians consider themselves all to be members of a rather private club and they'll exclude you from getting access to materials, access to patients, et cetera. They try to pull authority on

you. Fortunately, I can go right through that now. So that's one big advantage. But also, an M.D. is quite valuable—has been for me, anyway—when thinking about the basic science to understand the implications, applications, relevance to human health. Over the last thirty years, it has been enormously valuable to me in what I managed to focus on in terms of my own projects or a company's projects, or academic pursuits.

Hughes: Has there been any point that you regretted not having a Ph.D?

Martin: Not really. When I was at UCSF [University of California, San Francisco], I set up the M.D./Ph.D. program and ran it, even though I didn't have a Ph.D. It didn't make any difference. I think that's sort of the best evidence. I've been the thesis advisor for quite a number of Ph.D.s, so to me the really important thing is to acquire the knowledge and education that a Ph.D has.

Hughes: And you could get that.

Martin: You can get that, and I managed to get that without having to write a thesis. By taking courses at night at NIH, courses in the RTP when I was in medical school, and then courses that I either took or taught at UCSF, I ended up with the same type of coursework, and of course worked in the lab of which much training consists of the Ph.D. is. I believe it's critical to have the education and not shortcut the education, but the degree, as a second degree, I don't think is terribly important.

Hughes: I didn't ask you why you decided to specialize in medicine.

Martin: Probably because of the influence of Jim Wyngaarden. It seemed like more of an intellectual discipline than surgery. I also enjoyed surgery and there were a number of surgery faculty and residents trying to recruit me into the surgical internship program at Duke. I probably could have gone there, but I had this influence of a mentor who convinced me that medicine was more intellectual. The alternative was pediatrics, and I think maybe the fact that my father was a pediatrician pushed me away from that. I also felt that in terms of role models at that time there were more physician-scientists who were internists than pediatricians.

Hughes: Or surgeons, right?

Martin: Or surgeons, certainly. I mean, there are some, for sure. So I decided it would be better company to be among the physician-scientists within the internal medicine field than other fields. The other area that I thought about was neurobiology or psychiatry, because it was apparent that there was a real opportunity that was going to develop there. I thought about that and decided that I didn't want to go there because most of my classmates who were going into psychiatry were crazy as loons; I didn't particularly want to be associated with that type of nuttiness and neuroses. So I stayed away from it.

Hughes: Well, at NIH of course you met for the first time, Gordon Tomkins. Had you known him before then?

Martin: I had not known him before that. In fact, I went up to interview and he wasn't there. He was supposed to be there, but he wasn't, which was typical of Gordon.

Hughes: He'd found something more interesting to do.

Martin: I showed up at his lab and he was out of town or something. So Ed Rall, who was running that institute at the time, the NIAMD [National Institute of Arthritis and Metabolic Diseases] knew that Gordon had a slot and, because of Jim Wyngaarden's influence, just gave me the slot. Jim had known Gordon, so between the two of them they finagled me into the slot. I showed up a year or a year and a half later, something of that sort, and Gordon said, "Oh, I thought you were coming next year." He did that every time anyone showed up. "Oh, I thought you were coming next year," because he never had space. So that was my first contact with him, when I showed up to work.

Hughes: But he made space.

Martin: Oh yes, of course.

Hughes: Tell me about him.

Martin: You probably have talked with other people who knew him.

Hughes: I have.

Martin: He was a remarkable human being. Quite an inspiration in terms of his love of science, his love of life, his ability to really motivate people in science. He was quite remarkable because he was so enthusiastic about science and he had such breadth of knowledge. Very creative man. His creativity really exhibited itself probably most effectively in looking at data. When one would have an experiment that failed, as most experiments do, and you go sit down and look at it and if the data were good—that is, they looked reliable, et cetera—his ability to turn it around and say, "It didn't fail. Your hypothesis is wrong. This is what's going on, look at it this way." That learning to look at data, and accept it if the data are reliable, then creatively trying to understand what it's trying to tell you or what it <u>is</u> telling one, I think was a quite remarkable strength that he had. Then, jumping a few thoughts ahead, quantum leaps of knowledge and saying, "Why don't you think about this?" That, to me, was his strength.

Hughes: Can you explain those abilities by his previous education or experience? What was that?

Martin: Well, he had a very good science base. He had an MD and a PhD. He was mostly interested in science. To a great extent because of his charisma, personality, et cetera, he extracted an enormous amount of knowledge out of other people by talking with them, showing his enthusiasm for what they were doing. As a result, they would take great ends to teach him what they were doing. So his breadth of knowledge, whether it be x-ray crystallography or endocrinology or genetics or what have you, he had just sucked it all in. He was just sucking it out of everybody, out of the environment. He was doing it in a way that people loved to sit and talk with him, because it was obviously a two-way exchange. He was sucking it out of them, but he was also giving a lot of feedback. That was an enormous advantage he had.

Hughes: How much contact did you have with him at that stage, in his lab as a young person?

Martin: I worked in his lab right across from his office with his technician. His technician and I shared a lab bench and there was a postdoc on the other side, so it was a two-module bay. I had a lot of contact with him. When he was in town, I saw him many times a day, because he was in and out of the lab a lot.

Hughes: He would be looking over your shoulder at what was going on?

Martin: No, he wasn't that detailed. When you got data, and particularly if it didn't work, I'd always find time to talk to him and vice versa. I'd make an effort to go talk to him; he'd find the time to sit and look at the data. If it were positive, he could usually sense the excitement and be there. So there was a lot of exposure to him. His lab was not huge at that time. He probably had maybe eight or ten postdocs. No graduate students, because NIH didn't have graduate students. There were occasional summer students, but they usually worked for the postdocs. He had one technician. After I was there for a year or so, I had a technician but he was running what was by today's standards a small lab. He was head of the Laboratory of Molecular Biology, and there were another eight or ten faculty members, if you will, who were there in the Lab of Molecular Biology. [tape interruption]

There was a group of other scientists, senior people at NIH who had permanent positions, research professor level. It was also quite a remarkable group of people that he put together over about the previous six or seven years. That included Bruce Ames, Bob Martin, Todd Miles, David Davies, Marty Gellert, Michael Yarmolinsky, Max Gottesman, Harvey Itano, who were just world-class scientists. They were all right there on two floors of the small building.

Hughes: And interacting?

Martin: Very much so. I could interact with any and all of them. The coffeepot was between Gordon's office and the lab right across the hall where I was working, and so I could constantly find people at the coffeepot. We had all sorts of lab meetings, seminars, and journal clubs. That was a really intense three years that I was there. Beat the hell out of putting on a uniform and going to Vietnam, which was the alternative.

Hughes: Was this pushing you further towards the research end of medicine?

Martin: Sure, absolutely. My father visited once, I remember, and met Gordon and told Gordon he was trying to convince me to go back to West Palm Beach and practice medicine. Gordon told him that he'd be nuts to encourage me to do that. He shouldn't. He should just let me go pursue an academic career in research. My father walked out the door and Gordon immediately showed up. He said, "Don't let your father talk you into doing that." He felt that; he had no ulterior motive other than just trying to train physician-scientists.

Hughes: Well, and recognizing that he had something pretty good in David Martin, I'm sure.

Martin: But the group of people who were there as postdocs, the group was quite remarkable. I still see a number of them. There are at least two them out [in California]—one of them has moved back to the East Coast, but a couple of them came out with him after I did.

Hughes: Let's see. This is the mid- to late sixties? How prevalent was molecular biology at NIH? Was this now the going thing, that it was not an arcane interest any longer?

Martin: What happened is that the definition of molecular biology has evolved, and now when you say molecular biology most people think of it as being cloning and expression and things of that sort. At that time, it was essentially using biochemical assays to try to understand molecular function, mostly focused on proteins and making proteins. At least with bacteriophage, there was some genetics going on. Some with bacteria, almost no mammalian-cell genetics. Gordon had developed an interest in the response of mammalian cells to steroid hormones, particularly glucocorticoids, and so I was working in that field, which was sort of a new application of what we knew about molecular biology to mammalian cells. Once I was in his lab, I never subsequently worked on prokaryotes or even lower eukaryotes. It was always working with mammalian cells for the rest of my career until now, when I've returned to bacteriophage.

Hughes: That was a bit unusual, was it not?

Martin: There were not a lot of people doing mammalian-cell molecular biology in culture. There were a lot of objections. People would object to it: "Oh, you're working with cancer cells in culture? It may have no relevance to regular cells. Why are you working on that?" I heard some of that when I came to UCSF, some objections that the systems we were using were artifacts. I moved out here when Gordon moved out as well, so he and I were both working on mammalian cells. My argument was, "Well, you stick to your whole mice or rats if you wish, but I'm going to do ten times the number of experiments that you are, and I'm going to have more reliable data. Once I have my hypothesis proven by cell culture, I can quickly prove a corollary in an animal. You can't approach things that way by doing whole-animal stuff. And if you're going to work on bacteria, then I'm going to tell you it has nothing to do with mammals anyway." One had to be a bit on the defensive for a few years.

Hughes: What about the biohazard issue? Did that come into the issue at all at that point?

Martin: Not at that point. Not until cloning appeared was there any concern about biohazard. We were working with cancer cells, but the ones that I was working with at NIH were rat cells, and at UCSF primarily mouse cells. So we weren't worried about inoculating ourselves with the cell. [tape interruption]

Hughes: Do you have more to say about NIH before we move to UCSF?

Martin: It was a wonderful experience. In addition NIH had a very good graduate program with formal courses that one could take in the evenings. If one wanted to, one could use the credits towards a PhD at [Johns] Hopkins. I took courses almost every semester, two or three courses, in some of the hard science, particularly in advanced biochemistry that I had not had a chance to do in medical school or at MIT. I was taking quantum mechanics, advanced chemistry, some physics, some statistics, genetics. That was all really an important part of my experience. There was no requirement to do it, but everyone was doing it. All of the postdocs were taking those programs.

Hughes: Sounds like a busy life.

Martin: It was busy. But it was fun. It was intellectually very stimulating.

Hughes: Is your wife a scientist?

Martin: No, she's not. She was trained as a nurse at Columbia but is not a scientist. She actually hated nursing. She's a painter. After we moved to San Francisco she pursued her MFA.

Hughes: Oh, I see. So you got your humanities a different way.

Martin: Exactly right. She's certainly interested me in art. She received her MFA at the Art Institute here in San Francisco twenty years ago.

Hughes: So some parallels with Tomkins in a different way.

Martin: Absolutely. And we still see Millicent frequently. Art and science are a very interesting, important combination.

Hughes: I can imagine.

Martin: A lot of common aspects from a creativity point of view, even the necessity of having tools to work with. But the creative endeavor has to go beyond having and perfecting the tool set. However, one can't express much creativity without a set of tools. There are many similarities there.

Hughes: I hadn't thought of that before.

Martin: I certainly have seen people in science become infatuated with tools, but never use the tool to ask an important question. I think there are certainly artists who do the same thing. They have a technique and they never really become particularly creative or seek the relevant truth using the tool. Instead, they just express the tool. So there are a lot of issues there that are common interests between Kathy's interest in painting and mine in science.

Hughes: Do you find in your interaction with the art world that it's easy enough to sell the idea that science has a large element of creativity?

Martin: I think it is, so long as you can spend more than five minutes with the person. In five minutes, you can't do it because so many artists are completely ignorant in terms of science and they don't understand the field or the process. If one will take the time to listen to a description of the process and the experience of repeated failures before ever having a successful experiment, then fine artists will begin to identify with that, that the process is remarkably similar. It's all the same brain; left brain, right brain type of thing that's easy to explain to someone who's familiar with all that. If you talk with an experienced fine artist who's honest, they'll tell you about all their failures. I can empathize with that and vice versa.

Hughes: Interesting.

All right, the move to San Francisco. Were you following along after Gordon?

Martin: Yes, in effect. I looked at other jobs. Gordon decided first of all that he was going to go to Yale. He accepted the chairmanship of biochemistry at Yale. Then about a month before he was supposed to show up, he resigned.

Hughes: What was that about, do you know?

Martin: He didn't want to go to Yale. The former chairman there was clearly going to make his life miserable because he wasn't going to get out of the way. So Gordon resigned from that. He upset a lot of people. Then he was offered the chair at UCSF, and I think he also accepted that and resigned before he ever showed up. That was for a different reason; he did not want to be burdened with administrative responsibilities. He really wanted to be involved in the lab and in science. I don't know who, but someone scared him, I think appropriately so. He was not a good administrator. He could do whatever he wanted to, but he didn't want to do it, therefore he wouldn't do a very good job of it. So, enough of that. They were looking for a chairman for several years at UCSF and finally Bill Rutter took it. Bill, I think a day or so after he accepted the job, showed up in Gordon's lab at NIH to recruit him. He knew that Gordon had been in the Bay Area before, and that he was interested in going back to California. Very smartly Bill came to NIH and recruited him. Bill signed Gordon up on the spot, I believe. It was exactly what Gordon wanted to do. When I realized Gordon was going to leave NIH, I didn't want to stay on there as a postdoc without him as a mentor, so I looked at jobs at UC San Diego, Duke, and UCSF. Jim Wyngaarden at that time was back at Duke. Jim had offered me a very nice job at Duke and Gene Braumwald had offered me a job at University of California, San Diego, and I decided that I didn't want to go back to Durham.

[Tape 2, side A]

Martin: Ultimately I decided to come to UCSF. I was offered a primary appointment in the department of medicine with a secondary appointment in biochemistry. The first year while I was an instructor in medicine and biochemistry, I set up Gordon's lab, hired technicians and so forth, got the lab running. Spent about a year there, and then Hibbard Williams who was heading medical genetics in the department of medicine at UCSF took the job as chair of medicine at San Francisco General Hospital and moved. He left his lab and that position open and Holly Smith offered me both. I moved my lab out of Gordon's and over to the department of medicine, keeping an appointment at the department of biochemistry.

Hughes: Did that loosen your ties with the department of biochemistry?

Martin: Not really. Bill was chairman and I was still very much involved in the faculty, teaching, and recruiting. I saw Gordon a lot; he lived in Mill Valley; we lived in Mill Valley. We carpooled along with Barbara Levison, his senior technician for a year or so, and then he and Barbara started a commute bus from Mill Valley to UCSF. That was another interesting phenomenon because we all got to ride in this bus together, didn't have to worry about driving. It helped a lot with family life that Kathy knew when I was going to walk through the door rather than trying to deal with carpool timing.

Hughes: And it also meant for sure that you were going to be talking to each other. I guess you had been in the car, as well.

Martin: Right. So that was a good move.

Coming to UCSF, my expectation was that I would be here for a few years as a junior faculty member and then probably move on, which was the way a lot of faculty careers went after six or seven years, if you didn't make tenure, he or she went somewhere else and got tenure. After a few years I realized I'd probably made a mistake to come to San Francisco because it was such a nice place that I didn't want to leave it. I thought that I'd been better off going somewhere else first and then trying for tenure at UCSF.

Hughes: You had come from the exciting atmosphere of NIH. How was it in 1969, when you arrived at UCSF?

Martin: The exciting thing there was that primarily Bill Rutter and Gordon Tomkins were now going to build a biochemistry department. It had been a quite weak department prior to that. There was some deadwood there, but importantly they had positions that they could recruit into. They started recruiting some very good people. I don't remember the order in which they joined us, but Howard Goodman, Brian McCarthy, Reg [Regis] Kelly, came in the early days.

Hughes: Keith Yamamoto was a student.

Martin: Keith was a postdoc with Gordon. John Baxter came out from NIH a year later.

Hughes: Did he come because of biochemistry? Because he was also in medicine, was he not?

Martin: He had a joint appointment, as I did.

Hughes: But Rutter and Tomkins had largely been responsible for recruiting him?

Martin: Gordon was. He had been a postdoc in Gordon's lab for a year before Gordon left, but his Public Health Service commitment was for two years, so he couldn't leave. He had to stay on for a second year at NIH before he moved out. Gordon just convinced Holly Smith to recruit him.

Hughes: Did you have a lot of interaction with him? Your joint appointments were identical, right?

Martin: Yes, but I had more interactions with him at NIH. I guess I had been there for a couple years when he came in and I helped him get started in the lab. He had not had much basic science training when he started. He had been at Yale, as I recall, but he had just gone straight through medical school. I spent a lot of time talking science with him, helping him with techniques, et cetera. I didn't talk to him much over that year when I was here. He went into endocrinology and I used to see him frequently in the biochemistry department, more than anything else.

Hughes: You also had clinical responsibilities, presumably. Did that preclude you from being quite as active a member of biochemistry?

Martin: No, because my clinical responsibilities were an afternoon a week in the medical genetics clinic. That was a good situation because Charlie Epstein was head of medical genetics and pediatrics, and most of the patients we had were children. Charlie had a group that administered the clinic, and I didn't have to do any of that. I could just go, learn, teach, and see patients. Then I attended only one month out of the year on a general medical ward.

Hughes: So you really were predominantly a basic scientist.

Martin: Absolutely. I saw medical genetics consults, but I could control that volume. I could see as few or many consults as I wanted, and when I was on service and teaching, I used to increase the consulting activity. But the rest of the time I did not run a very active service. It was great. Holly did a great job of protecting me from having to do too much clinical work.

Hughes: Why do you suppose he did that?

Martin: Because I think he was wise enough to know that anyone who was really interested in basic science and was trying to build a career in science could be severely distracted by clinical responsibilities. That is a serious problem with academic medicine now, because now generating revenues is so critical. At that time, it wasn't so critical.

Hughes: Holly Smith had been one of the figures at UCSF that recognized that basic science needed to be improved.

Martin: Holly was critical in getting Bill Rutter and Gordon Tomkins to UCSF. There were three faculty members who came in the middle sixties who were key at that. It was Bert Dunphy in surgery, Holly, and Mel Grumbach in pediatrics. That was the early intellectual radius of the new UCSF.

Hughes: Maybe also Stu [Stuart] Cullen?

Martin: Cullen was dean there for a while, but he was—

Hughes: He wasn't particularly behind that effort?

Martin: He was not part of the real intellectual power there. Fran [Francis] Ganong was there as chairman of physiology, or became so about that time. Fran ended up being a pretty significant influence, but I think it was the clinical departments that recognized that if they were going to have a first-class medical school they had to have first-class basic science departments. That attitude was something that didn't exist early on in the late fifties when the decision was made to take what had been a split medical school between Berkeley and San Francisco and move it to San Francisco. The powers in that medical school at the time were the clinicians, who refused to move to Berkeley because they had lucrative practices in San Francisco. They had little or no appreciation for basic science, and it was Holly, Mel [Melvin Grumbach] and Bert Dunphy that changed that.

Hughes: What about Julius Comroe?

Martin: He was certainly a critical figure. He was probably the most prominent scientist at UCSF at the time, before Bill and Gordon came in.

Hughes: It was sometime in the fifties that the CVRI [Cardiovascular Research Institute] was founded. I don't remember the exact date.

Martin: Yes, it was he who started it.

Hughes: Was that a fairly focused activity?

Martin: Yes.

Hughes: I know that Comroe, at least eventually, emphasized joint appointments but it didn't seem to be having much effect on biochemistry, for example.

Martin: It was mostly physiology. He was a pulmonary physiologist and so his primary appointment was in the department of physiology. The CVRI was—UC has a name for it. It's an independent institute that gets direct funding from the Regents, I think, rather than through the school.

Hughes: I know what you're talking about. Right. [An Organized Research Unit—ORU.]

Martin: But all the faculty members had to have an appointment in a department of the school. Almost everyone there had an appointment in physiology or in medicine. There were a couple probably in surgery. It had little influence on the biochemistry department.

Hughes: So you had little direct tie with CVRI.

Martin: Very, very little. There were people whom I interacted with in the department of medicine; Dick Havel, for example, I knew pretty well and had a good rapport with. We had some common biochemical interests, but Dick, for instance, did not have an appointment in biochemistry. His basic science appointment was in physiology, even though what he was doing was lipid metabolism.

Hughes: Why do you think that was?

Martin: It was probably an historical accident. Physiology was a stronger department than biochemistry when Dick arrived. I think biochemistry, with sort of the new guard coming in, also didn't have a lot of respect for either microbiology or physiology as basic sciences departments or for their faculty, with the exceptions of [Herbert W.] Boyer, [J. Michael] Bishop, and Leon Levintow, who were in microbiology.

Hughes: The molecular people.

Martin: Well, but they became molecular people. At that time they were virologists. Boyer was a bacterial geneticist.

Hughes: But with a very molecular orientation, wouldn't you say?

Martin: Oh, absolutely. In fact, Herb didn't get tenure in the microbiology department. Ernie Jawetz, who was chairman of the department at the time, had no appreciation for what Herb was doing with restriction enzymes. Bill and Gordon did, so they worked out a deal with Ernie that they would take Herb into the department of biochemistry if Ernie would allow him to take his space with him, so they didn't have to give him new space. That was back in the middle seventies.

Hughes: I'm trying to think—it was about the time that Genentech was formed, I believe.

Martin: It was a little before that. That was probably '74, '75, something of that sort.

Hughes: I can find that easily.

Martin: It was probably '74, '75, I would guess. Herb became a [Howard] Hughes [Medical Institute] investigator, as I did. Then, when he started Genentech, shortly after that, they took it away from him. So that was '76, '77 they probably took it away from him. I think he became a Hughes investigator after he joined the department of biochemistry.

Hughes: I think you're right. Why did they take it away from him?

Martin: They were, and still are, anal about conflict of interest and profit motives. So they took it away from him; they also took it away from Stan Prusiner because they didn't understand what he was doing [prions]. They thought it was sloppy science.

Hughes: Well, they were a little wrong about that.

Martin: They were not always right.

Hughes: I want to get into all those issues around commercialization, but let's first turn to the biosafety committee, which was created in the summer of 1976. You were made chairman. Why do you suppose that was?

Martin: Why was it created, or why was I made chairman?

Hughes: Actually, both.

Martin: The biosafety committee was mandated by NIH at the time, because of Asilomar in '75. In '75, I don't think I was doing much in the way of cloning at the time. I was doing a little bit, but not much.

Hughes: Do you want to look at your bibliography? Gene expression. [consults his bibliography]

Martin: I think it was primarily that I didn't have a major conflict of interest by having to approve my own activities at the time. No, I don't think I had any. I think the first thing we cloned and published was '78. It was a matter of having someone who understood the technology well enough to read proposals, as well as not to have to approve my own projects when I was made chairman. The other issue, I think—which is one that may have been subtle and even subconscious—was, again, when one starts to talk about safety, it's primarily human safety. Being a physician helps a little bit. Maybe I know what safety is.

Hughes: I'm sure. Particularly in the UCSF context.

Martin: Exactly.

Hughes: I'm looking at a letter from Brian McCarthy to Dean Krevans, March 1975. It's obvious that he's writing in the wake of Asilomar, which after all was February of 1975, just the month before. He's talking about the need for what then is being called a biohazard committee, which—I think, somewhat significantly—was later called the biosafety committee, and you're one of the five people that he recommends.

Martin: Brian was also one of the fairly early recruits that Bill and Gordon had brought in. We were talking about Reg and—

Hughes: He, at that point, was not doing cloning. Or was he?

Martin: Brian was not doing cloning. He had been involved also in a lot of messenger RNA purifications, but I don't think he was cloning at that time. He was on the biosafety committee, as I recall. I think he was a member.

Hughes: I have that letter. The faculty members he recommends are Steven Cohen or Keith Hadley. I know Hadley. Those are people who are in microbiology. That must be the rationale?

Martin: Yeah. Steve, as a physician-microbiologist, ran the clinical microbiology lab at UC, so he understood infectious diseases. He was not only an infectious disease physician, but a bacteriologist as well as a physician.

Hughes: One of the criticisms that arose around the whole biosafety issue, that molecular biologists in general did not have microbiology backgrounds and consequently didn't know the safety techniques.

Martin: Or in general, didn't know anything about infectious diseases and the consequences of safety lapses.

Hughes: The implication is that they had a rather cavalier attitude towards possible hazards.

Martin: Right.

Hughes: Then Christine Guthrie in biochemistry, she said pointedly: "A bacteriogeneticist not involved in plasmid research," which I guess is the same thing as saying "cloning research," isn't it?

Martin: Yeah, she was studying tRNAs.

Hughes: And then the third are "David Martin or Jay Levy, Medicine, whose experience with malignant cells and oncogenic viruses is appropriate."

Martin: Jay is a virologist and physician.

Hughes: So there it is. I don't know why the powers that be—whoever that would be—would that have been [Julius] Krevans?

Martin: It would probably be Krevans, then.

Hughes: Made the decision? I've got a letter of your appointment, actually signed by Leslie Bennett. That doesn't necessarily mean that he made the final decision, although maybe he was part of it.

Martin: Leslie—did he sign it as Academic Senate, or something?

Hughes: He signed it as Vice Chancellor of Academic Affairs.

Martin: That's the other Leslie Bennett, not the one that you know.

Hughes: Not the one in pharmacy, no.

Martin: Two T's and two N's—different Leslie.

Hughes: The original members of the committee, which is, of course, later expanded—and you're right about McCarthy—Albert Jonsen was the ethicist, Christine Guthrie, Howard Goodman, Louis Diamond.

Martin: Lou Diamond, that's Jared Diamond's father.

Hughes: Oh, yeah.

Martin: He was a remarkable—he's dead now—he was a remarkable man. He was a pediatrician who retired from Harvard at age seventy-five and took an appointment at UCSF and spent the next twenty years at UCSF, getting R01 grants, did a lot of research on Rh incompatibility. He discovered RhoGAM and Diamond-Blackfan syndrome. He was a very astute master physician and scientist from an earlier era. Very, very sharp. Wonderful judgment.

Hughes: Which explains his appointment.

Martin: Absolutely.

Hughes: There's Steven Cohen, who you mentioned. James Cleaver?

Martin: He's a radiation biologist who's still at UCSF. A PhD, discovered the defect in xeroderma pigmentosum. He was doing DNA repair biology.

Hughes: So probably he had the knowledge that comes from the safety procedures that grew up around radiation, right?

Martin: Could be. Right, but he was also interested in DNA and DNA repair. He knew something about DNA, although he wasn't cloning at the time.

Hughes: And Herbert Boyer. I don't think we have to explain his presence. What was your understanding of your responsibilities?

Martin: Well, it was primarily to put into place a process to oversee the use of recombinant technology on the campus, and to judge as best we could whether there were risks and what the risks were, and essentially whether projects or experiments should be permitted or not permitted, for safety reasons.

Hughes: And looking to the guidelines mainly as your—

Martin: As they evolved.

Hughes: —as your means of judging one way or the other?

Martin: Right.

Hughes: Because it was still obviously very early days. The whole risk-benefit issue is the nub of it all, isn't it? And there's no conclusive answer.

Martin: There's no one answer. It was just a matter of trying to use reasonable judgment from science and clinical and political perspectives to guide what was going on and not going on.

Hughes: Can you take yourself back to that period and try to recreate how real—or not—you felt the potential danger to be?

Martin: [pause] I don't think I ever felt that there was an extraordinary danger associated with just recombinant technology. I thought the danger was probably greater working with animal viruses than it was with just recombinant molecules. I can remember presenting some talks about recombinant technology and pointed out that in many ways recombinant technology could reduce the danger or potential hazards associated with virology. I used as an example, smallpox. I proposed that the smallpox genome be broken into pieces by restriction enzymes, that the different pieces be deposited in different places and that the whole virus be destroyed. That would obviously allow one who could gather all those parts to reconstruct the virus if we ever needed it as a vaccine or for any type of necessary research, but on the other hand it greatly reduced the potential for abuse—as the disease had been, by that time, eliminated—or for accidental outbreak. It wasn't very long after that there was an accidental outbreak in the U.K.

So I was quite positive about it, because it was controllable rather than uncontrollable as viruses are, particularly viruses that recombine, as they do. At the time, we didn't have everything that's on the front page of the papers now—with influenza vaccines or SARS [Severe Acute Respiratory Syndrome] moving from one species to another and finally into humans by recombination.

Hughes: You didn't even have AIDS [Acquired Immune Deficiency Syndrome] yet.

Martin: That's right. So <u>there</u>'s the real danger. I can remember saying that I can't think of an organism that could be created that can do more damage to humans or to the planet than do humans. You can't make anything any more damaging than our species.

Hughes: [laughs] It's true.

Martin: It's really true. So I continually tried to put it in perspective, and I think much of it was making certain that people weren't knowingly doing things that appeared to be stupid or unduly risky, or that would cause a political uproar, just by something getting into the press that looked bad, or sounded bad, or a bad sound bite. So that was more of a concern than the actual risk.

Hughes: And of course that happens, but I think by then—are you gone, are you on sabbatical by then? I'm thinking of the episode where the "wrong" plasmid was used in the insulin experiments.

Martin: I got out of town after it happened. After I knew about it, but before the uproar.

Hughes: And you were probably very pleased to be out of it.

Martin: Very pleased to be out of town and have a eight-hour time change from here to there, so it made it difficult for reporters to get hold of me. Again, that was a situation where it was the rule; it had nothing to do with the safety. It was a very confusing situation between what was an approved vector and what was a certified vector. NIH had it really confused, and there were some letters that were exchanged between Hans [DeWitt] Stetten and myself.

Hughes: I've got one of them.

Martin: I tried to clarify that. One can make a very good case that it was an honest error. One can also make the case that it was the result of some cavalier attitudes that sort of jumped the gun on use of vectors.

Hughes: There was other evidence of cavalier attitudes as well. I don't know if you remember the article that was published in *Smithsonian* magazine, by a reporter who spent some time in the Boyer lab?

Martin: Oh, yes. I remember that. It was a young woman.

Hughes: Yes, Janet Hopson was her name. She essentially was writing about the culture of that lab, but part of the culture of the lab was a certain cavalier attitude towards the safety issues. Of course, with the general political context being what it was, it was rather an explosive thing that happened. That would have been during your time on the biosafety committee. I think that article was written in '76.

Martin: I think it was published while I was on sabbatical.

Hughes: Oh, was it? It could have been. I thought it came earlier than that, but I might be wrong. I don't have it here. But you don't remember having to deal with that specific issue?

Martin: I remember that there was flak, that Boyer's lab was lax, and people were upset: How could the biosafety committee let this stuff go on? My perspective was that part of our purview was not to inspect labs, it was to review projects.

Hughes: And that was true, wasn't it?

Martin: Yes. The investigators were on their own in terms of enforcing lab safety, but we were not a policing entity at all. We were a reviewing entity.

Hughes: What political clout did—

[Tape 2 side B]

Hughes: I hadn't noticed this before, but these are minutes from September 1976[1]. The entry is "Monitoring of facilities." It says that "The members are well aware that the charge of monitoring facilities and approving grant proposals will introduce other spin-off responsibilities, such as ascertaining adequate safety procedures and personnel training. Although it is the primary responsibility of the principal investigators to enforce the safety guidelines, it is the role of the committee to increase the awareness of potential risks at all levels." So, in theory I guess, if you were aware of problems that were within a specific lab, you were supposed to call them.

Martin: You couldn't ignore it, but on the other hand the feeling was that we shouldn't, we couldn't really find the time or the resources to proactively go out and inspect labs the way OSHA [Occupational Safety and Health Administration] does, or something like that.

Hughes: I don't know whether this was your idea—you asked for a survey of the faculty using protists, as you put it. Was that your idea, or was that something that was mandated?

Martin: I don't remember. We certainly did inspect—and I inspected several times—the P3 [Physical Containment 3] lab.

Hughes: Which was in biochemistry?

Martin: Right, it was in biochemistry. It was right around the corner from my own lab, so it was easy for me to go by there, and I did. Periodically I went in and made certain it was neat and clean. I had a key to it.

Hughes: That was another area where there were problems, remember? Where people were not entering in the logbook.

Martin: That was related to those same accusations. Mostly Axel [Ullrich] using approved but not certified [plasmids], and/or not entering on the log activities for which it was being used.

Hughes: [producing document] This is at least one of the survey forms. Does that look familiar?

Martin: Yes.

1.Francis A. Sooy, MD, Chancellor to Deans, Directors and Department Chairmen, October 11, 1976. (UCSF Library, Archives and Special Collections, AR 86-7, folder 87)

Hughes: Do you think you composed that?

Martin: I don't know. I wrote "protists" up there; that's my handwriting. Both of those are my handwriting.

Hughes: I don't recognize most of those names. Are they lab heads?

Martin: Yes, but it was pharmacology. They were doing very different type of work. This is just—

Hughes: One.

Martin: One department. Everybody in the department is listed there.

Hughes: Did you ask that of everybody in every department?

Martin: I presume so. Departmental chairmen, institute directors, that's the directions. It was Frank Sooey who was chancellor at the time.

Hughes: The campus could not have helped but be aware of the political context. How overtly were you stepping carefully, because you had not only what was happening at the national level, with the legislation before Congress, but of course the state was also getting active. They were a little bit behind the feds. Then some neighbors of UCSF were also concerned. It was a sticky position that you all were in, I would think.

Martin: My attitude was very much let's do the right thing, but let's not overreact or allow anyone else to overreact in this process, because it's more political than it is substantive. So there was a level of awareness there, certainly. Part of that was trying to use Al Jonsen to help us figure out from an ethical point of view, how to deal with politics, because that was a little closer to the political realm of activities then than was basic science. I think most of the community concerns ended up later relevant to the Fireman's Fund building, where they really became up in arms—[tape interruption]

Hughes: You mentioned that there were problems. What were they, around the Fireman's Fund building?

Martin: That was years later where there was a real community uprising against UCSF putting laboratories in the Fireman's Fund building.

Hughes: Is that Laurel Heights?

Martin: Yes, Laurel Heights. On California Street. I think that was much more of a political uprising than what was going on in the earlier days. There was a little bit of activity in the neighborhood about recombinant DNA. I think we considered putting a layperson on the biosafety committee.

Hughes: I think you had to.

Martin: Eventually we had to. I don't think initially we had to, but I think subsequently there was a layperson put on. But it was not a requirement initially. The idea was to try to

open it up so that it was clear that the public had access to the proceedings and there were no secrets.

Hughes: I see in these particular minutes T. Mellon, who I believe was the CAO [Chief Accounting Officer] for the city, was that it? Doesn't ring a bell?

Martin: Sounds a little familiar.

Hughes: And then there was a man, I think he had just retired as head of San Francisco Department of Public Health.

Martin: Oh, yes.

Hughes: What is his name? I have it here somewhere. We can add it later. Currey.

Martin: Currey, yes, Currey. He was on it.

Hughes: I think he may be the layperson you had before you had to have somebody. That was interesting.

Martin: Right.

Hughes: So there's no doubt that you were aware that there was a political dimension to it.

Martin: Oh, yes, absolutely. I mean, after Asilomar, it was undeniable because of the response there. Although most people who organized Asilomar lived to regret it, at least most of them publicly eventually said, "We overreacted. We probably shouldn't have done that."

Hughes: I've heard historians argue that the publicity given to Asilomar also promoted the science, that scientists who otherwise may have taken longer to get on that bandwagon because of all the press that was given to it, may have jumped on the bandwagon sooner.

Martin: That could be. I did not go to Asilomar. Gordon Tomkins went and I remember his coming back and saying the amazing thing about this meeting was not the regulations, but was related to what you're saying. That is, this stuff is really working. It's really amazing what we're going to be able to do with these tools. He was very excited about learning more about the tools. At that time in his lab there was no recombinant technology.

Hughes: Who was doing it in those early days? I've heard, for example, that Rutter himself took a while to take on recombinant DNA.

Martin: The people in the early days who were at UC—Herb [Heyneker] in Boyer's lab was involved, Howard Goodman was involved. There was Peter Seeburg, who was a postdoc in Baxter's lab, was involved.

Hughes: Ullrich, of course.

Martin: Axel was a postdoc in Goodman's lab. There was a fellow by the name of Raymond Pictet, who was in Bill's lab. He was a cell biologist, but he was involved in dissecting the islet cells from the pancreas to get access to the insulin messenger RNA. That was Bill's early connection, through Raymond and his interest in pancreatic differentiation. It was mostly that set of postdocs plus Boyer and a couple postdocs in his lab who were actually doing the work.

Hughes: Such as your friend Herb [Heyneker]. I guess that was later, wasn't it? Nineteen seventy-six, seventy-seven?

Martin: Herb was there in '75.

Hughes: That's right, he was a UCSF postdoc from '75 to '77.

Martin: His thing was ligase. When he was a graduate student he had purified DNA ligase and brought it with him [from Holland].

Hughes: Brought it with him. One of his swifter moves.

Martin: That's right, because without it, cloning wasn't going to work.

Hughes: Was Howard Goodman brought into the department because he already was using recombinant DNA technology?

Martin: No, Howard was brought in because he had developed electrophoretic methods of purifying and sequencing RNA. People were sequencing RNA rather than DNA at that time.

Hughes: Why was that?

Martin: No one knew how to sequence DNA. Gilbert and Maxam—

Hughes: Maxam's sequencing method was introduced in '77, I think.

Martin: It was a couple of years after that. So Howard had one of the few methods of trying to get at sequence data. He was brought in, set up this huge, very expensive electrophoresis room that was a hell of a lot more dangerous than any recombinant DNA technology, because you could actually get electrocuted with this high voltage system they had. He and Boyer started collaborating, trying to understand what the restriction ends were.

Hughes: They had a formal collaboration, did they not? Was that unusual?

Martin: They had some common grant support. In fact, they were both [Howard] Hughes investigators, and Hughes was putting money into both of them for this collaborative project.

Hughes: It was the Hughes money, the Hughes grant that was the basis for this collaboration, because remember later there's a falling out.

Martin: I know Hughes put money into it, but I don't know how much NIH put into it, or NSF [National Science Foundation]. I just don't know what those economics were. But I know that Hughes was funding it to some extent because we would go to Hughes meetings together and talk about what was going on. So I know that was formally being supported that way.

Hughes: We're running out of time, aren't we? Is there more to say about the actual reviewing of the experiments? I have one example that's a little bit difficult for me to interpret. It's not even clear to me who is submitting this. Is it perhaps the Boyer lab?

Martin: [looking at document] "Collaboration with Goodman and Ullrich. Cloning the cDNA of murine and bovine insulin mRNA." That sounds like Rutter.

Hughes: And Rutter signs it, but I thought that was just because he was chairman. But not necessarily?

Martin: I think this was his, because he was working in *Xenopus* and pancreas exocrine enzymes. He was doing a little bit himself on yeast. He had perhaps one person in his lab working on yeast.

Hughes: Was that heading towards the hepatitis business?

Martin: Not yet.

Hughes: So give me a feel for what happened when something like that came to the committee.

Martin: We would usually pass it on to the committee members, then we would meet and discuss it, and going through the technical aspects, determining whether the vectors were approved or not approved or certified or not certified, where it was going to be done, whether it was mammalian message or not mammalian message or yeast or what have you, because all of those altered the containment requirements. If you look, you'll see that the only thing that's requiring a P3 are mammalian genes. The rest of them are P1 or P2.

Hughes: Would there be much discussion?

Martin: Yes, something like this, usually someone on the committee who understood it and was not involved would walk the rest of the committee through it in terms of how it fit into the guidelines and whether the containment was appropriate, whether it happened to be a forbidden experiment, et cetera. There were some—I forget just what they were—but there were some forbidden experiments that one simply couldn't do. They mostly, as I recall, had to do with using human sequences and putting them in certain vectors. So there would be certainly effort put into each application. It was never a rubber stamp. We didn't know what was stampable and not stampable, because we were still feeling our way through it.

Hughes: As time went on—I forget what the date is here, is it '77? Seventy-six, I think. You alluded to the poor communication in those early days.

Martin: With NIH.

Hughes: Did that get better?

Martin: That got better as it was formalized and the RAC [Recombinant DNA Advisory Committee] published its minutes more rapidly and communicated them to labs. There were not a whole lot of labs in the country that were using this. The RAC office was set up by this time, and were presumably communicating, but some of the communications were phone calls and not things published in the Federal Register, for example.

Hughes: Would that have been your responsibility to keep up with the latest?

Martin: Yes, but in many cases the principal investigators were keeping up with it better than even I was because they were practicing it. They were not necessarily looking for regulations, but they were looking for new tools. As soon as something was approved, they raced to it.

Hughes: They raced to it. [laughs]

Martin: They wanted to be the first ones to use it.

Hughes: I can well imagine. I think we have to stop, because it's on the dot of noon by my watch.

[End Tape 2, side B]

Interview 2: February 3, 2004
[Tape 3, Side A]

Hughes: We've skirted around the issue of recombinant DNA technology, particularly in reference to your heading a committee at UCSF, but I didn't ask you when you first began to be conscious of it. Was it after your arrival at UCSF, or had you heard of it before?

Martin: Well, it didn't exist before '69.

Hughes: That's true, because you were there early.

Martin: It didn't really exist until early seventies. People began to realize what was possible, so I think the first I heard about it was a discussion probably with Herb Boyer. That involved Herb and Howard Goodman talking about some of the things they were doing, and then discussions about what Herb and Stan Cohen were doing.

Hughes: You mean, while they were beginning, the first experiments were going on?

Martin: Right. PSC101 [Stan Cohen's plasmid, used in the Boyer-Cohen experiments]. The Department of Biochemistry had, every Thursday afternoon at 5:00, an informal faculty meeting just to talk about science and not administration or administrative issues. Those would usually go on an hour, hour and a half, something of that sort. Everyone took turns talking about what they were doing in their labs. I can remember some of those discussions. Howard was talking—and at that time in the early days of that, as I think I mentioned last time, Herb was not in the biochemistry department. He was in the Department of Microbiology. It was somewhere in the vicinity of '73, '74 that he moved to the Department of Biochemistry, because he had gotten an appointment in biochemistry with tenure.

Hughes: But he, before that, had been going to these seminars, had he not?

Martin: He had generally not been going to the biochemistry seminars. At least, I don't think so. He would give seminars; I can remember his giving formal seminars about restriction modification genetics in *E. coli*, and that was in the early seventies. I can remember it being interesting, but I didn't imagine where the utility would be. But certainly Bill Rutter and Gordon Tomkins and Brian McCarthy realized that there was something there, that it was an interesting biological phenomenon, but I don't think it was really until Stan and Herb began to apply it to episomes or these plasmids that Stan was isolating and characterizing that people began to understand what could be done with it, with the sticky ends. The whole trick was the sticky ends.

Hughes: Was it pretty obvious at that point that this was a breakthrough?

Martin: I think it was obvious that it was a neat technique that allowed one to splice pieces of DNA together and therefore potentially genes. I don't think people quite realized initially the implications of that in terms of either using it to generate or manufacture proteins in a microorganism that normally didn't make them. That came a little bit later, and I'm not sure exactly how that evolved. It probably was only a few months until

people began to realize the implications of it. Then the issue of "Can you do anything commercially with it?" I don't think was appreciated until probably after Bob Swanson had the discussion with Herb and they came up with the idea, "Let's build a company around it."

Hughes: Actually, I found evidence that Herb was thinking loosely about it before then.

Martin: He probably was.

Hughes: Yeah, and in fact had even approached—I think it was actually the lab that later sent over [Peter] Seeburg and Axel [Ullrich], trying to get some DNA synthesis capability.

Martin: The lab at UCSF?

Hughes: No, it was somewhere in Germany.

Martin: I don't know where they were, actually.

Hughes: I should know that. Might have been Heidelberg. I can't remember. I have it, because I've talked with Axel. I just can't remember it anymore. [laughs] But as Herb tells it, he was just baffled about how one goes about to form a company. And you know, he was busy. His lab was just a beehive at that point, so I'm guessing that he didn't put too much energy into it until Swanson came out.

Martin: Until Swanson set it out, right.

Hughes: First of all, one question about your previous statement: you emphasized the splicing aspect. Do I gather from that that the cloning wasn't quite as obvious to people? I mean, that isn't what they grabbed on to?

Martin: Well, I think the cloning was a consequence of being able to splice; that one, could excise a gene and splice it into an episome or a plasmid that could then self-replicate. That was where the cloning came from. It could be put into a bacterium that would then make a whole lot of copies of itself. So the cloning was a consequence of the splicing, but the splicing was the first step in that.

Hughes: Did people make that conceptual leap right away though?

Martin: They probably did. I just don't remember when or where I first heard of that leap. It was probably in the very early seventies when people were just beginning to think about splicing and what one could do with it. The key was, I think, that these episomes carrying antibiotic resistance that Stan was working on, were capable of self-replicating in the bacterium. That way, one could make a lot of copies in the bacterium. If the bacterium also multiplied itself, then that was all the merrier. But I do believe it was really the culmination of a self-replicating element into which had been spliced a piece of DNA of interest that made people realize they could purify genes and replicate them, acquiring one could possibly want of a pure piece of DNA, whatever it contained.

Hughes: That seems to have been the emphasis in the early seventies of [Paul] Berg and other people at Stanford. It wasn't so much the cloning until Stan came along. It was more of the splicing.

Martin: Splicing, yes. It was splicing into SV40.

Hughes: How unusual was it to use a plasmid as the vector? Because people like Berg were using viruses.

Martin: Stan was in a situation in which, because of his medical interest in antibiotic resistance in infectious diseases, he was well aware of these episomal elements in bacteria that carry antibiotic resistance, and that episomes were both replicating and being transferred horizontally from bacterium to bacterium. I think he just happened to be really well primed to understand that there was this element that existed that behaved like a virus, if you will. Whereas I think that Paul may well have been aware of these episomes, but wasn't thinking about them. He was thinking more about the viruses that have their own replication origin and can replicate in an animal cell.

Hughes: His was pretty much an SV40 lab at that time.

Martin: He was at that time, right.

Hughes: I'm just thinking, though, how you and Stan mirror each other in terms of your appointments. At that time, I guess he had an appointment just in medicine but he was going to all the biochemistry seminars and using their enzymes. You know, a lot of interaction. I know you had the two formal appointments, but your interests were broadly similar.

Martin: I knew Stan at Duke, actually, when he was a resident.

Hughes: Oh, that's right.

Martin: I was a medical student and he was a senior resident, as I recall. I had him as my resident at one point. Got to know him fairly well, realized he was interested in science, and vice versa. I had just come out of the RTP when I met him, doing my senior medicine rotation—my only medicine rotation, because of the RTP. So we both recognized that we had an interest in basic science, and then I was surprised in the very early seventies to learn that he was at Stanford. I had a few conversations with him at that time. I spent some time in the early seventies teaching at Stanford and ran into him down there. When he and Herb were collaborating, I knew Stan pretty well.

Hughes: Better than Herb?

Martin: Not better than Herb, because at that time Herb and I and our families were sharing a ski cabin in Tahoe, back in the early seventies, probably '72-'73 or '73-'74. For a couple of years we had a cabin and would ski together. So I knew what Herb was doing at that time, but that was a little before he and Stan had really kicked it off.

Hughes: They talk about collaborating in November of '72 when they both meet at a plasmid conference.

Martin: That was I guess about the time.

Hughes: But you were talking about science in between the ski runs?

Martin: A little bit, yes. I mean, it's hard to avoid that.

Hughes: Yeah. [laughs] That's what preoccupies you people.

Martin: Absolutely. That's right.

Hughes: Before we really get into your move to Genentech, I wanted to have you talk about the beginning commercialization of academic research that is happening from the mid-seventies on and perhaps is first to come to a head at UCSF, where we have, of course, Genentech, and later, Chiron, and other companies being formed. Of course, it caused a stir. Can you take yourself back to those days and remember what you were thinking and observing?

Martin: I think the most heated discussions in the early time were actually occurring in those Thursday afternoon biochemistry faculty meetings. Herb was in the biochemistry department at the time, before Genentech was formed, maybe a year or so, something of that sort. He offered at one of those Thursday afternoon sessions to sell essentially founders shares, common shares in Genentech to any faculty member who wanted to take it up at a nickel a share, and a thousand dollar minimum. I went home and told my wife about it. I didn't have a thousand dollars, and I said, "You know, if I had a thousand dollars I'd probably put it in." No one took it up. I don't think there was a single person who participated in that. Then there was a cadre of faculty members who objected conceptually to that, and in fact proposed that Herb not teach. [tape interruption]

The group, there were a few of them, maybe three or four who were upset by the idea of commercializing and did not like what Herb was doing. Didn't like the concept. At the time, Herb was lecturing in the biochemistry department. I can remember the proposal that he not be allowed to teach because he was becoming commercially oriented. I can't remember what the details were, but he also made a faux pas in one of his lectures and made some comment that was off-color, and <u>that</u> just added fuel to the fire. There was a lot of consternation at that point; people wanted to ostracize him, sort of because he was setting it [Genentech] up. At that time he was also a Howard Hughes investigator, so that the Hughes people also became upset because he owned a lot of stock in Genentech and they saw that as a major conflict of interest. It was fairly nasty for a while. Those who were the most vocal about it, as I recall, were Christine Guthrie and Keith Yamamoto. There were a few others, but I can remember <u>they</u> really didn't like it. They held onto that position for many years; that is, that faculty members should not be involved in commercial endeavors, shouldn't hold stock. Wasn't too long after that, in the late seventies, that Bill started Chiron and that really upset the apple cart because he was chairman of the department and Bill had provoked a fair amount of animosity among other faculty members for other reasons and so that just gave them more fuel. John Baxter started Cal Bio[technology], about that time. There were all sorts of issues going on within the faculty about commercialization. I think without exception they've all come around and changed their tune about commercial involvement.

Hughes: Even Keith.

Martin: Even Keith. In fact, Keith was interesting. When I was at DuPont Merck—this was the early nineties—Keith was still pure and hadn't consulted, didn't own any stock. We had a project there that I thought Keith would be useful for, so I had one of our senior people call him and ask him if he would consult for us. He agreed to, and they invited him out. He arrived one evening and they were taking him to dinner, so I joined them for dinner. Of course, I knew Keith really well and knew his position and he knew mine. So I walked into this small restaurant in Wilmington, a nice restaurant. I walked up, looked at the table where he was sitting, company people around him, and he was now a consultant. I said, "You whore! What are you doing this for?" He was speechless, which was unusual. I loved teasing him, but that, I think, was the turning point. It was not very long after that that [David] Goeddel started Tularik and recruited Keith as a major consultant, and Keith resigned from the DuPont Merck consulting position so he could go put all of his commercial endeavors into Tularik. It took more than a decade for him to convert, if you will.

Hughes: What were you thinking at the time, when this was breaking in the seventies?

Martin: I was not terribly disturbed about it, I guess. I can remember in one instance on the biosafety committee, Herb had applied for permission to do some recombinant experiment in his lab. I can't remember what it was with. It may have been with somatostatin or one of those Genentech had been formed. He was going to grow up some bugs expressing a recombinant gene. I remember explicitly including in the approval that under no circumstance could any of the material that he was going to make in his lab be used for commercial purposes. I just wanted to make certain that we kept it squeaky clean, that an academic lab was not being used to manufacture anything that had commercial value. That's about as far as I went on that. It did influence my decision to go 100% to Genentech —not so much Herb's, because Herb never worked at Genentech, except during a sabbatical in the 80s. But John Baxter worked part of his time at Cal Bio, I think a day a week. When I decided I was going to go to Genentech, I essentially cut it very clean and decided I would go a hundred percent and not maintain any activity at the university. I wasn't going to have a foot in each camp it and be subject to criticisms of conflict of interest, loyalty, et cetera.

Only one issue that ever came out of that. Obviously, I gave up my Hughes investigatorship but I had a number of NIH grants. UCSF let me take them to Genentech and use Genentech as an off-campus performance site, but they wouldn't let me renew. I can remember getting into an argument with about three people on the faculty about why they wouldn't let me renew my grant. They let me use what I had. The one who was the most vocal about it was Ira Herskowitz. Ira, I thought, was being unreasonable. He was another one who was really anti-commercialization; he was very pure. Ira and I had a falling out over that and I thought he was just very annoying because he was being holier-than-thou in his position that, "No, we can't let you renew it because you're abusing the university to do that. You're using us." I said, "Look, I teach here. I'm teaching medicine, I'm teaching biochemistry. You don't pay a cent for it. I'm generating revenues for the Department of Medicine for you. You're getting the overhead. I'm not taking the overhead; the university gets the overhead. So don't tell me I'm abusing the university. I'm not. I've got postdocs. We have fellows at Genentech." We had fellows from the Cancer Research Institute. So that was very

annoying that he was drawing this line. At the time I think he was vice-chairman of the department. I think maybe Bill was still the chairman; I've forgotten. Anyway, Ira was another one who was very anti-commercialization, but I certainly decided I was going to cut it very clean and not have a foot in each camp in terms of salary or appointments. I was already an adjunct professor because of the Hughes funding, so I just cut that tie.

Hughes: Another subject, before we leave UCSF, is the Division of Genetics, of which you were a member. You came to UCSF in the sixties when there was still—according to the archives, anyway—a lot of debate going on about whether the university would support founding an actual Department of Genetics. I wondered if, as you came in, this was something that you were cocking your ear towards. Did this make any impact? Did you follow that debate?

Martin: I don't think so. I probably wasn't even aware of it at the time. When I came in, I was in the Department of Medicine, and there was a division of medical genetics in the program of medicine. Hibbard Williams was head of it, and then a year after I was there, Hibbard went over to County [San Francisco General Hospital] and so I took his position as head of medical genetics in the Department of Medicine, and Charlie Epstein was head of the same division within pediatrics. So Charlie and I started interacting in medical genetics, but there was not a department of genetics. There were plenty of people who were qualified to run a department of genetics or be in a department of genetics, and I think that there was some discussion about Herb being in the department of genetics rather than a department of biochemistry, but it just never materialized during the time I was there.

Hughes: Was that unusual for a medical school in the late sixties, not to have a department of genetics?

Martin: I don't think so.

Hughes: No? Why would that be?

Martin: The people who were doing genetics were doing bacterial genetics. There was almost no somatic cell genetics in the late sixties, and in a medical school most of the genetics was human genetics. There were a few significant departments of human genetics in medical schools, but usually they were not pure departments of genetics. Chicago had one, as I recall. [Johns] Hopkins had Victor McKusick's Human Genetics Department. There was a Department of Genetics, I recall, at Oregon and a Department of Genetics at University of Washington that was quite well known. But most of those departments of genetics were more in the graduate programs rather than part of a medical school per se. They might be in the department of biology in a liberal arts school or a science school, not in a department of genetics at a medical center.

Hughes: There was a Department of Genetics at Berkeley.

Martin: Oh, absolutely. And Berkeley didn't have a medical school.

Hughes: Exactly.

Martin: And Stanford, I think, even then had a Department of Genetics. I'm not sure, but I think they did.

Hughes: Yes, because [Joshua] Lederberg was chair.

Martin: But I think that that department probably preceded Stanford Medical School moving down to Palo Alto.

Hughes: I think you're probably right.

Martin: So I think most departments of genetics were really basic science and had very little to do with medicine before graduate training in genetics. And most of it was bacterial genetics or fungal genetics. Duke had a department of genetics when I was there. It was bacterial genetics and fungal genetics, *Neurospora* genetics. The people who were teaching in that rarely taught in medical school. There was one of them, I recall, who gave an infamous lecture when I was a sophomore. He was a very smart guy and his opening sentence of his lecture was, "As far as I'm concerned, humans are nothing more than a seventy liter test tube." So that was the entrée to genetics. There were several that wanted to boo him, but didn't have the guts to.

Hughes: What about the Division of Genetics, which of course as you know, ends up in the Department of Biochemistry?

Martin: I don't remember very well, but I believe that that was something that occurred about the time that Herb came in.

Hughes: I think it was to accommodate his move to biochemistry.

Martin: That's right. At the time that that happened, Mike Bishop and Leon Levintow, I think also became members of that Division of Genetics in the biochemistry department and ended up with joint appointments in microbiology and biochemistry because of that division. Herb moved completely into biochemistry, so he was in biochemistry in the Division of Genetics.

Hughes: He was head of that division, at least for a time.

Martin: He may have been.

Hughes: How did it function? You were in it; did it make much difference to your life?

Martin: No. I didn't even know I was in it.

Hughes: Yes, you were in it, according to the documents anyway.

Martin: It didn't mean anything. It was part of the biochemistry department and all the administration and budgeting—what there was coming out of the university—was done through biochemistry, rather than any type of direct divisional—I don't think they had any revenues of any sort. They were not in an organized research unit under the Regents, like the CVRI or the CRI. It was semantic only, I think.

Hughes: And consequently wouldn't have been seen as a threat by the Charlie Epsteins of the world who already had an established operation?

Martin: Charlie might have been bothered by it; probably was. I know Charlie really well and he tends to get bothered by those things. I think he was also a member of it, but he didn't have an appointment in the biochemistry department. That was something that bothered him for years.

Hughes: What were the reasons for that, do you think?

Martin: Political. Just pure politics. Here was a physician who was practicing medicine and who wanted an appointment in biochemistry. People just weren't willing to give it to him. Stan Prusiner suffered the same thing. For years Stan wanted an appointment in biochemistry, and the powers that be wouldn't give it to him.

Hughes: You think it was largely the MD? Because Prusiner, perhaps more than—well, I don't know that much about Charlie Epstein, but I don't think of him as being such a basic scientist; I think of him more as a clinician. You could argue, on that basis, what would be the rationale for giving a clinician a joint appointment? But Prusiner, despite the fact that he was a MD, as far as I remember had a large basic science effort going on.

Martin: Not any more than Charlie.

Hughes: Is that so?

Martin: Charlie had a quite significant mouse developmental biology/genetics program going on in his lab.

[Tape 3 side B]

Martin: He had probably as large a lab as anyone had in the Department of Pediatrics.

Hughes: I stand corrected, then.

Martin: He was trying to do genetics in mice at that time. He had trained with Chris Anfinsen at NIH doing protein biochemistry and refolding, then moved into human genetics. I remember when Jay Seegmiller—who used to teach human genetics at NIH in the night graduate program in the—left to go to UC San Diego, Charlie took over teaching human genetics in that program. So he had an interest before he came out to UCSF. He was certainly trained as a basic scientist. Stan had trained with Earl Stadtman, and had less basic science training than Charlie did. His research at UCSF was certainly at the time significantly less basic. He was working on transport across the blood-brain barrier; the transport of amino acids, as I recall.

Hughes: So none of the prion stuff.

Martin: That had not started. That started probably in the late seventies, and he had also been a Hughes investigator in the late seventies. Hughes didn't feel his science was up to snuff

and pulled his investigatorship. As I recall, Julie [Julius] Krevans, Holly Smith, and of course, Bob Fishman, who was chairman of neurology—had a lot of faith in Stan. I think Julie ended up getting him some tobacco company money to support him when the Hughes pulled out. He was working on prions at the time when Hughes pulled out.

Hughes: Then maybe was that the answer, partially?

Martin: Yes, they didn't believe that prions as pure protein could be infectious. He was headed in the direction of claiming that he couldn't find the nucleic acid, and basic scientists didn't believe him. Again I believe a lot of it had to do with the fact that he was an MD trying to do basic research, didn't have the qualifier that is a PhD. I think a major reason I was fairly well accepted in the Department of Biochemistry is that, while I had a MD, I trained with Gordon Tomkins. He was a very influential person there and vouched for me, gave me some credibility that these others who in many cases were as well or better trained than I, simply didn't have. I was publishing in reasonable journals, participating in the Thursday afternoon sessions—I was very conscientious about that, because I learned a lot and that helped with relationships.

Hughes: Yeah. I'm sure it helped immensely. Both those things.

Martin: The department of biochemistry is pretty political. I think part of that had to do with some history, in that the department of biochemistry before Bill and Gordon showed up was a quite weak department. There were one or at most two people who were good scientists there. Yang, who was a very well-respected physical chemist, was chairman for a while. There may have been another one or two, but most of them were not particularly well respected. There were quite a number of joint appointments that people had in the basic science departments. Bill cleaned house and terminated all of the joint appointments—and I think rightfully so—to try to build up a quality, reputable department that didn't have either deadwood or joint appointments by people who really weren't qualified.

Hughes: Actually, there's one more topic before we move to Genentech, and that's your membership in RAC, Recombinant DNA Advisory Committee. Just to remind you, if you need it, you were there in 1981 through 1985, which is kind of interesting to me anyway, because it overlaps your academic and your corporate move. Why were you appointed, and how did that whole thing happen?

Martin: I don't know who suggested that I be on RAC. I would guess it was probably Jim Wyngaarden. He was head of NIH at the time. After I joined, I realized that what they didn't have any physicians who understood human genetics, human medicine, and basic science. So I think it was probably having that combination of experiences plus Jim Wyngaarden as a mentor that resulted in my being me nominated or appointed.

Hughes: Do you think your heading up of the biohazard committee at UCSF came to anybody's attention?

Martin: It could have. Yes, I would guess it probably did, because that occurred before. Hans Stetten, I guess—RAC was under Stetten and I got to know him fairly well through Gordon back in the early seventies. He was a fairly frequent visitor to San Francisco at that time because he was very interested in what was going on scientifically. I can't

remember when I was appointed whether it still reported to him or directly reported in to Jim. I don't remember, but they had set up the office. I do remember during all the controversy over certified versus approved vectors that Hans was the person with whom I had a fair amount of formal correspondence at the time, so that probably had something to do with it.

Hughes: He was head of the RAC? Because I get confused about all these committees. There was also some governmental interagency recombinant DNA committee, but that was another group, wasn't it?

Martin: I'm not sure it was. I think it was the same group, because sitting on RAC—maybe *ex officio*, but I'm not sure it even was *ex officio*—were people from the FDA [Food and Drug Administration], for example. I don't think there was anyone from DOD [Department of Defense] or DOE [Department of Energy] at that time, but there were a couple of other government employees who were certainly attending, and I think they were members. Henry Miller was on it for a while, and then someone else came on it from FDA. I don't remember who it was. So other governmental agencies were represented on RAC. I don't remember there being another intergovernmental agency but I could well be wrong.

Hughes: I can check that out, anyway. Do other members stand out in your mind? How cross-sectional was it?

Martin: Irv[ing] Johnson was on it, and that's where I first met him. I subsequently met him at Lilly while I was at Genentech. So there was someone on there from industry. Richard Novick was on there. We briefly overlapped. He's actually a MD, but a very good *Staph*[*olococcus*] *aureus* microbiologist who's at NYU. David Friedman, who's at Michigan, was on it. Who else? Several other people whom I got to know a bit, most of whom I hadn't known but had known <u>of</u> before joining. It was an interesting time, certainly. Bill Garland was head of the Office of Recombinant Technology and chaired the committee. Oh, Susan Gottesman was on there, as I recall.

Hughes: Can you generalize about the tenor of the discussion?

Martin: I don't think anything was going on that shocked me or surprised me at those meetings. We had a gene therapy subsection, as I recall. I think I chaired that for a while, but I felt that—and I was wrong—that gene therapy was going to be coming along much faster than it did. I kept warning the committee, "You really need to prepare for this. You need to understand what hurdles you want to put up, how you're going to regulate this, and what role the FDA is going to play in this." I can remember having a number of discussions about that. I was working on some things in my own lab at Genentech on a NIH grant, actually, and I thought things were going to move faster there than they did. So I was saying, "I think in six to twelve months you're going to see an application here and there's a lot of work to do." So I can remember having that discussion. I think maybe they had better insight than I did, the other members, and just dragged their feet about setting up any criteria for approval. I also knew French Anderson, at NIH—in fact, from taking night classes at NIH—and knew what he was doing fairly well.

Hughes: And he was working at that time on gene therapy?

Martin: Right.

Hughes: What about—don't I remember right—isn't his name Cline, at UCLA? Didn't he very early on try gene therapy?

Martin: In Israel.

Hughes: Was it in Israel?

Martin: Yes. He tried it in Israel, but he got his hand slapped here for it, because he was sending materials to Israel from UCLA. Marty was the person I met first when I came to UCSF as a recruitee. He was in the Cancer Research Institute and they had a position available. I can remember Marty taking me out to dinner in Chinatown. Then not very long after that he and Dave Golde left, or he left and Dave Golde left subsequently. Yes, he tried to do something in a thalassemia patient. As I recall, tried to put hemoglobin genes in. That was a real outlier: no approval, no one was prepared for it. He became a persona non grata after that.

Hughes: Initially I thought that might have been a prompt for RAC to do something, but if it was a complete boondoggle maybe they said, "See, we told you, the time has not come."

Martin: That occurred early. I would bet it was late seventies. I don't think I was on RAC at the time.

Hughes: Well, as kind of a segue into Genentech, although I want you to tell that story in full, let me ask you though, when your job title changed, when you moved to Genentech, and of course were now really focusing on the commercial end, did that change your argument, your position at RAC?

Martin: I don't believe so. I remember when I made the decision, my RAC membership had no influence on my decision. But I did, after I decided to move, call Bill Gartland and told him what I was planning to do and I asked him whether that was going to affect the position. His response was, "No, I don't see why it should since we already have Irv Johnson on there who's from a pharmaceutical company." It was clear at the time when I went to Genentech, that Genentech was not going to pursue gene therapy. I did not believe it could be made commercially viable for a long time, if ever. So I didn't have any intent on doing it, except under my continuing NIH grants, which I just moved to Genentech.

Hughes: But you were with a company that certainly was having to deal with RAC.

Martin: Right, but not gene therapy. RAC, yes.

Hughes: Not gene therapy—

Martin: Well, I didn't have to deal with RAC, because we were not using federal funds. At the time RAC had purview only of federally funded project, and everything else was voluntarily.

Hughes: But I thought Genentech went out of its way to comply—

Martin: We did for political reasons—The FDA had jurisdiction over our clinical trials, but the RAC did not have jurisdiction over what Genentech was doing. But we made public statements that we would conform to all the RAC requirements in terms of containment, but we did not report everything, because a lot of it was proprietary. We just simply said, "We will conform and abide by."

Hughes: There was a stink about that. I don't know if it was Genentech specifically, although I wouldn't be surprised if it had a voice in it, but as the companies began to be founded there was worry that, in complying with RAC review, proprietary information would get out.

Martin: Right. I remember that, in general, but I don't remember personally any experience with the idea of the academic RAC experience or the Genentech RAC experience. I certainly remember some dialogue, but I don't think that Genentech ever submitted any type of proposal to RAC. I could be wrong; they may have in the early days, but I don't believe they did. Herb did, through the biosafety committee.

Hughes: It was kind of a fine line, wasn't it—

Martin: Sure.

Hughes: —that Genentech was not going through RAC in terms of its research proposals, but it was telling the world they were complying? But it was sort of complying under their own terms, right?

Martin: That's right. Bob Swanson was smart enough to realize that if he did not comply that he would be subjected to all sorts of, not only criticism, but maybe regulation and be ostracized from the commercial world in some way, or the financial world. So he was pretty adamant about publicizing that Genentech would comply. That preceded my joining Genentech; we certainly maintained it while I was there. I was on RAC maybe for a year before joining Genentech [1981–1985], and during that period of time the requirements for submission to RAC certainly changed. It evolved and became much less onerous, much more relaxed, and to a great extent delegated to the local biosafety committees. RAC just became less of a problem, taking to primarily reviewing of animal, human genes, and a virus that would infect humans—that type of concern about building a monster that could infect humans to which there would be no immune response. The focus changed, and gene therapy became part of it.

Hughes: This may have been before your time, but do you remember any discussion about the ten-liter limit?

Martin: Oh, yes. I remember the ten-liter limit. But there were also qualifiers around that; it was ten liters for certain circumstances where containment was required, but once one had done a couple of experiments and demonstrated safety and/or the splicing was between organisms like a human growth hormone and *E. coli,* that disappeared. I don't know the specifics of how it disappeared, but I know that doing a ten-thousand-liter fermentation at Genentech was never a problem because of what we were putting in the fermenters.

Hughes: Yes.

Martin: Ten liters is about all one person could carry.

Hughes: I think it was Stan [Cohen] that told me that, and it was in the warm-up to Asilomar when there were—in his case, the plasmid committee; I may be wrong that it was he—but anyway it was somebody on that committee that sort of arbitrarily said "Okay, we've got to have a limit. What do you think? How does ten sound?" [laughs]

Martin: Right, that was probably true. I was not on the committee at that time. I can remember knowing the regs forwards and backwards from the UCSF Biosafety Committee. There was clearly a ten-liter limit there, and I thought the ten-liter limit was just something that an individual could probably comfortably carry and not be at high risk of dropping it. Because if you say fifty liters, it's hard to carry fifty liters around. Ten liters you can move around.

Hughes: That may have been part of the thinking.

Martin: Could have been.

Hughes: Okay, finally Genentech. Tell me about your thought process, particularly, and how the offer arose. That whole story, please.

Martin: I knew about Genentech, obviously, from the press and from the faculty bashing of Genentech and Herb. I knew many of the people who had gone there out of Herb's lab, Howard Goodman's lab, Baxter's lab. [Peter] Seeburg, Axel [Ullrich], Art Levinson—all of those people, I knew, mostly postdocs in the department of biochemistry, the ones who were publishing, anyway. So Herb asked me one day if I would suggest some names of some people to head research at Genentech. I gave him three or four names that I thought would be interesting. He came back to me, a couple of weeks later and said he'd gone around and asked others the same question and one name that kept coming up from other people was mine; was I interested? I told him no, I didn't really think so, and he said, "Why not?" I said, "Oh, you know, I'm enjoying what I'm doing. I really enjoy the breadth of what I'm doing, other science—the biology and medicine. I think that it would just be too narrow, cloning and expressing." He said, "Well, you know, it's actually much more complex than that. There are all sorts of scientific challenges and problems that have to be solved as you start to scale up, and they're all basic science. So maybe what you ought to do is to see what we're doing and talk to some people down there."

So a month or so later—this was probably in the spring of '82—I went down and gave a seminar. I spent a day there talking mostly with the people that I knew and came away very impressed with the quality of the science, the quality of the people, and how much they were enjoying what they were doing. I also realized they were doing a lot of things that I didn't understand, and that I could learn something there. It looked like a place where people were having fun doing science. I came back; Herb asked me what I felt. I said, "I need to think about it." It was shortly before that or Genentech had been trying—I learned this from Herb after the fact—recruit Don Fredrickson as head of research, and for reasons that I'm aware of that should remain off the record, they decided not to offer him the job. My thought was, "Wait a minute, there's a guy who is really a very renowned physician-scientist, has run NIH and so forth and so on; was he really serious about that job? Maybe that's a better job than I'm giving him [Boyer]

credit for. Maybe it's not just some fly-by-night entity sitting in South San Francisco." So I started to take it seriously. Then at some point shortly afterwards I had dinner with Bob Swanson.

Hughes: Was that the first meeting?

Martin: No, that was not the first meeting. I had met Bob when I first interviewed there—

Hughes: Oh, of course.

Martin: —but I hadn't spent much time with him. So he and I had dinner, and I think at the time—I can't remember whether I had an offer in writing before I had dinner with him or after I had dinner with him, but I can remember at dinner telling him that I had a couple of concerns. One the breadth of what I was interested in scientifically versus what Genentech was doing, and I couldn't tell in the matter of a visit or two—how broad the science was. I had three concerns. The second was that if I went there, I would be tainted as I had seen tainted other faculty members who had left academe to go to industry, at that time the pharmaceutical industry. In general, most of them that I knew from UCSF who had gone that route had simply flunked out of academe. They couldn't get grants, they were physicians and simply had gone to clinical research in industry, and I just didn't want to be associated with that type of academic because I didn't want to be seen as a failure in academe, to go to industry. And the third concern was that if I did it and didn't like it, would I be able to get back into academe, or would I just have burned the bridge behind me? Those were among other things we discussed. His comment was, "Look, why don't we do this: We'll have a gentleman's agreement that you'll come for three years. At the end of three years, if you want to go back, no problem. We'll accelerate vesting of any stock that you have at that point, and no hard feelings, you can go back. You just have to figure out whether they'll take you back or not."

The other issue was the reversibility of it. I went and talked to Jim Wyngaarden about it and his comment to me was also influential, in that he said, "Well, look. I've just taken this job at NIH." He had taken it a year or so before that, I guess. "I'll make a deal with you. I'll do this for ten years, you do that for ten years, then we'll switch jobs." And I thought, "Wait a minute, would you really? Does it sound as if to you, it's really that important a job?" He said, "Oh, yeah, absolutely. If you go do that, then the experience you gain over the next ten years will really be valuable to NIH, because none of us have ever had commercial experience, and I know that would be useful." So I realized that maybe it wasn't irreversible if I went. So then I talked with the fellow Ken Wright, who was the administrator of Hughes. I had been supported by Hughes for eight years at that point, [1974–1982]. I asked him what his opinion was, whether it was reversible or irreversible, and his comment was, "If after three years you want to go back to academe, we'll provide you with a Hughes investigatorship. We'll give it back. We can't guarantee it will be at UCSF, because we may not have a slot there, but we'll give you a position at a good university and you can just pick up where you were and you'll have a full budget your first year."So that was interesting, because it meant that I could take a job that I had some concerns about whether I wanted to stay there or not, and yet not annoy people by being unloyal and deserting them after three. That was encouraging. I then spent probably the next month—or several weeks anyway—after I had a written offer—trying to decide what I was going to do. I went and talked with several people

about the issues of being tainted. The Fredrickson story did a fair amount in terms of convincing me that there probably wouldn't be a taint, or I didn't think Don would do it. I knew Don a little bit at that time through the Howard Hughes Medical Institutes.

Hughes: You couldn't have much more assurance than that, could you?

Martin: I decided it was reversible if I went to Genentech, and it may be really different than going to the pharmaceutical industry. During this entire time I was talking with Kathy about it, whether I was going to desert academe and go to industry. The other concern obviously, mixed into that, was that I truly appreciated academic values. I didn't want to compromise those, but I discovered when I went to Genentech that those academic values were there as well.

[Tape 4, Side A]

Martin: There was a lot of really good discovery going on, all generally headed in the direction of: How do you make products out of this?

Hughes: What did you think about the intellectual property aspect?

Martin: Well, I spent some time talking to Tom Kiley when I was down there on one of the visits and Tom described to me that on several occasions there were desires or needs of the scientists to make a presentation of recently generated data at a symposium. The patent counsel would write a patent [application] in a day or two-day and file a provisional. He said, "We will not let that get in the way. We'll just file early. We can always go back and fix it later," which is true of the U.S. patent system. So I became convinced that it would not be a real constraint, because of the way things were being handled and the pro-publishing attitude there, which Bob also expressed and believed. I think that, in fact, Genentech really changed that whole philosophy within industry about publishing, much to the consternation of many CEOs of other biotech companies. I can remember some discussions that occurred after I was at Genentech. People were very upset that we were publishing so much, because it really encouraged and stimulated their scientists to want to publish and they didn't want that to happen.

Hughes: Yes.

Martin: But we were setting a standard and then a lot of people took it. So IP [intellectual property] was not a problem, didn't bother me. I didn't know anything about patents; I had never filed a patent before I went there, but I had heard of people waiting thirty days, ninety days, et cetera. Not at Genentech, I don't think they ever did.

Hughes: Okay. So, after these various conversations and explorations, you decided to go?

Martin: So I did. I think it was maybe August that I decided I was going to take the job. I told Bob that I would accept the job and he said, "Okay, when can you start?" I said, how about next July? I discovered that while that's the way academics do it, it's not the way it's done in industry. He said, "How about next month?" "There's absolutely no way I can do that next month, because I have this lab, I have all these responsibilities, got

teaching responsibilities, so forth and so on." He said, "All right, how about January 1?" So we agreed on January 3 [1983], I think, but with the understanding that I would spend some time there during the fall, as much as I could spare.

Hughes: And you did that?

Martin: I did that. I did—I spent at least a day a week there, particularly when it came to budgeting time, because I had to budget for the next year.

Hughes: But you weren't participating in Genentech research at that stage?

Martin: No, I was learning about it, talking to people about it. I think I went to a few management committee meetings, but it was probably—I don't think it was more than a day a week at that time. I was very slowly putting my big toe into the water and trying to run my lab at UCSF, mostly.

Hughes: Did you just leave that? Did any of your people come with you?

Martin: I took my whole lab. I didn't move them for six months for the first six months of '83. I left my lab operating at UCSF and in July of '83 I moved the lab. I moved about six or seven people with me. Several of them were supported by grants as postdocs. In fact, I think initially when I moved maybe all but one or two I had support that continued for a year or two. I had three postdocs who, between January and July when I moved my lab, left to take faculty positions. I had three very senior postdocs, but I took at least three postdocs and two or three technicians, as I recall. A couple of postdocs remained as postdocs and at least one of them got an appointment as a scientist.

Hughes: Was it commonplace to have postdocs in Genentech labs when you arrived?

Martin: It was. There were quite a number of postdocs. That was something that was, I think, really very important, because that was sort of an academic value. We were teaching. We didn't have any graduate students, but we had postdocs and fellows. That was one of the things that I learned about. I learned the value of postdocs in an industrial setting particularly, and when I went to DuPont Merck there were no postdocs. One of the things I negotiated going in to DuPont Merck was a budget for seventy postdocs, and by the end of about the first eighteen months we had seventy postdocs. They completely changed the place. I figured I had to change the culture of that institution that postdocs were and probably the only way to change it abruptly in the right direction.

Hughes: Interesting.

Martin: So I took postdocs, technicians and one scientist to Genentech. That scientist, a woman named Ingrid Caras, was there up until about 1997 when I hired her at Eos [Biotechnology]. So she was at Eos until we merged Eos with PDL last spring. She ended up worked with me at UCSF, Genentech, and then eventually Eos. One of the technicians, who went to Genentech, Steve Withamb, went to Lynx [Therapeutics] after he had actually become a scientist at Genentech. This is a fellow with a bachelor's degree, used to be my secretary at UCSF. He became head of molecular biology at Lynx. He is a really smart guy. There were a number of people who went from UCSF to Genentech, and then I've even worked with them since.

Another thing that I did for which I took a lot of flak and people still laugh about it was a result of my family and I living in Mill Valley at the time. I'd been commuting by chartered bus to UCSF and we had only one car, for example, for at least ten years. I didn't want to move, and I didn't want to drive, because I'd been using the bus to read. So rather than negotiating a relocation package, I negotiated with Bob for a car and a driver, so for the next four years while we continued to live in Mill Valley I had a car and a driver that would pick me up in the morning and I could read all the way down. Pick me up in the evening, I'd read all the way back. People couldn't believe that someone at Genentech had a chauffeur. You know, it's a lot cheaper than making a down payment on a house for me or paying escrow fees even, so I had that for three years. That was part of the deal; for three years they'd pay it.

Hughes: Was that the main way you kept up with science on the broad scene?

Martin: On the broad scene was by reading, going to meetings, talking with scientists at Genentech.

Hughes: What did you find when you were actually settled in? What was new? Because I believe I'm right in that you were the first formal vice president of research; is that not true?

Martin: Right. Yes, it's true.

Hughes: There had been other people who had sort of—

Martin: Sort of played that role. There was a guy, a Swiss, with an Italian name.

Hughes: [Giuseppe] Miozarri.

Martin: Yes, who had been there—I think he was head of molecular biology, and molecular biology was king. So he was sort of head of research. As it broadened out, there was a pharmacology department and that wasn't part of research, so it became diffuse. Mike Ross played that role for a while, doing mostly administrative responsibilities, budgeting, that type of stuff. I think I went there with the title of vice president of research, and then not very long after that it became vice president of R&D—that is, we began to build up the development side.

Hughes: Do you know anything about why at that juncture, Swanson or whoever decided that this position had to be formalized?

Martin: The research position?

Hughes: Yeah. I mean, why then and at that particular time?

Martin: My response to that would be I was surprised they waited so long. Having been involved in situations like that it really requires someone to gather information and ultimately make decisions or designate someone to make decisions, and communicate to the rest of management and vice versa what are the priorities of what's happening or what's not happening. It was quite diffuse. Part of it may have been that there were too many people reporting to Bob, which is a common thing, that happens, and they needed to put some structure in. The research group was over two hundred people at that time.

Hughes: Was it that large? I would think it would also enter in that Swanson was not a scientist.

Martin: Bob set priorities, but he would not tell people how to do science. He'd ask a whole lot of questions.

Hughes: [consulting paper] Yes, you're right. 1983-1988, Vice President, Research, and then Senior Vice President, Research and Development, 1988-1989, according to your CV.

Martin: I'm not sure that's really correct, because I had responsibilities for development within a year or so of getting there. The "senior" title came for political reasons, as they usually do. That was, I had recruited Ralph Snyderman to head development. I had been head of R&D, and I recruited him to be head of D, as vice president. So he came as vice president of D, and I guess I reverted back to a vice president of research. He reported to Kirk Raab directly, and I was reporting to Bob. It became apparent after a while that it wasn't working, and so we ended up with a decision that Ralph had to work for me as head of R&D, and in order to convince him to do that we had to make certain it didn't appear to be a demotion for him. So I suggested we make him a senior vice president of development and I could stay as VP of R&D; I didn't care. So the decision was made, we'll give you both this "senior" title but he's going to work for you. So he accepted that for about a year before he went back to Duke. I think those titles were juggled for that reason. But I think it's really important and I've learned since—and it certainly worked at Genentech—to have one person responsible for R and D because the integration and the handoffs must be smooth and efficient.

Hughes: Is that the basic thing that was not working when you were reporting to Swanson or Raab?

Martin: Yes. And Ralph and I were good friends, but it just wasn't smooth. One person just has to be able to drive it. And I've seen that elsewhere.

Hughes: How much did each of you have to learn of the other field?

Martin: Well, Ralph had to learn about the specifics of the projects in research, but he had a good science training. He had probably more to learn about development than he had to learn about the research side.

Hughes: Is that so?

Martin: Development can be quite different. That was a real challenge to him. A real challenge for me when I went in there to learn something about development. And Mike Ross, who was a very fast learner, was more or less heading development for me when I was head of R&D. Mike learned it and Mike taught me a lot. But he had the degree deficiency. He didn't have a MD and therefore, trying to deal with clinical problems and issues within the clinical research group just didn't work, and that's when I took it over. Then I had all clinical reporting to me as head of R and D. Mike did something else within Genentech.

Hughes: Did you consider it a plus that you knew how to get into the development aspect, or was this just oh my God, this is what I have to do to keep this job?

Martin: I don't think it was what I had to do to keep the job; I think it was what I had to do to do my best to make Genentech successful. I had to take on that responsibility, learn it and do it right, and then try to integrate it. At the same time, my love was more for the basic science, the discovery side of it rather than the development side of it. I learned a lot about development.

Hughes: Yeah. Was there a shift that you had to go through? Putting it simplistically, most academic scientists are functioning pretty much as independent units. Now, all of a sudden, you're part of a team, where the welfare of the institution means the welfare of the individuals, to a large degree. What went through your head—if anything—about this? I mean, was it an issue you struggled with?

Martin: Oh, it was a big issue. I struggled with it and probably didn't do a particularly good job of it. In academe, it's a series of fiefdoms, and a team is two people, it's not two hundred people, four hundred people or something like that. So there was the issue of understanding not just how a team <u>should</u> work in a science or an R&D organization, but how to lead a team, how to evaluate a team, how to motivate it properly. The other aspect of that, which I think was really important but it took me a while to figure out—I think I never probably never figured it out while I was at Genentech—is how to deal with sort of the mass psychology of a lot of people, all of whom are highly motivated, energetic and ambitious, and aggressive. Certainly one never learns that in academe. You know how to deal with aggressive, ambitious people, but you're not trying to work with them or get them to work for you—maybe when one becomes a dean or a departmental chairman, but I hadn't done that. The biggest group I had led was a lab of postdocs that got up to about seventeen at one point. So it was a very different experience.

Hughes: Not only in size, I would observe, but also in status. There's no question that a postdoc is going to be in a lower position than you as lab head, where that may not have been as clear at Genentech. I mean, I should ask you that.

Martin: I remember one person saying to me one time, "Goddammit, I'm not your postdoc." I was telling him what to do. He's still a good friend of mine; I saw him a few weeks ago. That worked two ways. It was a two-edged sword, because, on the one hand trying to get people to do what your postdocs did was difficult. On the other hand, it was difficult to realize how much power I had in that position. I didn't realize if I asked someone a question, that many people would take it as a command, that "I better go do that." So I was shocked when people would go do something. "Why'd you do that?" "Well, you asked me to do that." "I didn't ask you to do that." So the response was, "But you asked me such-and-such and such-and-such." I said, "Yeah, but I want to know your answer. You decide. Don't make me decide for you."

So it was difficult in both ways to figure that out. I think I finally figured it out when I got to DuPont Merck because I'd had the experience at Genentech, and I had recognized plenty of my screw-ups at Genentech. Other people recognized them first, of course, and let me know.

Hughes: [laughs] That's usually the way.

Martin: Absolutely. I learned from some of those. When I left and decided I was going to take the job at DuPont Merck, I spent a fair amount of time trying to retrospectively look at what I had done right and what I had done wrong, whom I had learned from, whom I hadn't learned from.

Hughes: Can you generalize about those new insights?

Martin: I think that I was so cocksure of myself in making a very rapid analysis of data or a situation, making a decision and implementing it, that I made some wrong decisions, and I certainly annoyed a lot of people by doing that. I frequently would not give people an opportunity to say what they thought before, as Bill Young used to accuse me, I would shoot from the hip. Part of that was personality and experience, and part of it was also—someone pointed out to me once—the training as a physician where so frequently one is called on to make a decision at the bedside that you better make quickly and act on it or you're going to be in trouble, or a patient's going to be in trouble. So medical training reinforced that shoot-from-the-hip attitude. That was certainly one thing. The other thing which I did not appreciate, as I should have was the politics of the situation at Genentech—of working within a large organization.

Hughes: What are you thinking of when you say that?

Martin: Some of the things I did were stupid and some of them were simply naïve. Some of the stuff I did that was stupid was to be critical of things that were going on in manufacturing. Bill Young and I knew each other well through the management committee, and he was head of manufacturing. But I was pretty critical of some things that were going on and some power-grabbing that he had done in terms of fermentor access et cetera. And worse yet, I was critical in public, in front of the research group about the manufacturing group. That was just stupid. That was not something you can do if you're a member of a team or a manager, you can't polarize research versus manufacturing, because you really are interdependent. So that was one type of thing.

The other thing that I did in terms of being really naïve was I recruited David Botstein from MIT to join us full-time at Genentech, and my naïveté was not to realize what a political animal David is, and that his power struggle within himself would be his primary motivator for anything and everything he was doing within Genentech. I just said, "Hey, look. I've known David for years; smart guy, love to have someone smart like that here, let's go get him." He had been disappointed at MIT that they didn't give him the chair of biology. Bob was on the oversight committee at MIT at the time and got to know David. Bob came to me and said, "Do you know, David Botstein?" I said, "Yes." "What do you think; should we go recruit him?" So I went and recruited him. I found David to be a very smart guy, but very ambitious. Initially I didn't recognize it, but he was clearly politically trying to maneuver within Genentech to have my job. I just felt that I wasn't vulnerable. I didn't care what he was saying behind my back, because I felt that I could stand my own with him or anyone else in that position. His political maneuvering became so apparent to me that I figured it was apparent to everybody else that it was purely political, and so people would ignore it. But, they didn't.

Art Levinson was the same way. Art used to just go bonkers in my office, shut the door and say, "I can't believe what Botstein is doing!" Yet Art was savvy enough to catch on

and know how to deal with David's politics. David and I both left at about the same time. He went to Stanford and I went to DuPont Merck, but Art kept him on as a consultant and I think probably even to this day he has him as a consultant. He probably spends a day a week there. But Art was savvy enough politically not to let himself be undermined by David, and I think to some extent I got undermined by David. But I can also say that I learned a lot from him. He's a very creative thinker.

I thought, "What would David Botstein do in this situation?" I figured it out. I decided to organize by functional departments and then go interview people to decide who was going to chair each of those departments. I was then going to place them in those chairs, and then ask each principal investigator, of which there were fifty or sixty at that point to decide for whom and where they wanted to work. It was their choice. We were going to let them give us three choices, A, B, or C choice and we'll match each with the department chairs priorities. David was always one to express, "Let things go where they will go. Don't try to force them." It was sort of a genetics approach. Survival of the fittest. So I finally convinced [Joseph] Mollica that I should let that happen. I did that by going to talk with Roy Vagelos about why I thought it would work, et cetera. Roy said, "Oh, what the hell. Go try it." So he convinced Joe. I set it up. People couldn't believe it. "You mean, I get to choose where I'm going to work?" It was completely different. I said, "Well, you, as the PI [principal investigators], can choose, but you have to have discussed it with everybody in your lab, and you have to know what everybody else in your lab thinks and where they would like to go. But ultimately you can make the decision. We're going to do a ranked choice. I'm going to have the directors rank their choices, you rank your choices, then we'll match 'em." They just couldn't believe it. When I joined DuPont Merck, I found a difficult situation in that there was a DuPont pharma group, which consisted of hundreds of scientists. I don't really remember what the number was, maybe a thousand. And then there was another group in DuPont Central R&D that was not part of pharma at all. But part of the deal between DuPont and Merck was that they were going to merge the DuPont Central R&D Life Sciences group, which had a number of outstanding scientists in it, with the pharmaceutical group that had not been very productive. Merck was going to contribute a few people in, but not many. But it was probably that merger, money from Merck, and the name that were going to build this entity. I went in there not knowing how in the hell was I going to organize? We had this group of really good scientists plus, another group of mediocre scientists. I needed to put together an organization that functions well. I went to Wilmington about three months before the joint venture started to operate, to assess the situation.

Well, it worked. It worked like a charm. That's the type of thing that David Botstein was so creative about and would just say, "Let them fall where they're going to fall, and then they can't complain." There were two PIs who approached me within six months or so later and said, "I made a mistake." No one else—if they made a mistake—would ever admit it. So we ended up with a really nice, stable, well-motivated departments.

[Tape 4 side B]

Hughes: The feeling I get about Genentech, particularly in the earliest days, of course, is it was pretty freewheeling that these were scientists who were pretty self-confident, at least in

the new genetic technologies, considered that they were at the cutting edge. They were all more or less of the same age, they'd all more or less come to Genentech at the same time, and then a few years later, all of a sudden, they're reporting to somebody like you. I can imagine that there could have been some tensions.

Martin: Well, sure. It required building credibility. Credibility in that setting had to be scientific credibility; nothing else counted really, in their minds. So it didn't make any difference that Bob said, "He's the boss." That was not so relevant as that I understood what they were doing, I could be critical of what they were doing, critical with validity, and they would listen and I would listen. There were certainly moments. When someone says to you, "I'm not your goddamn postdoc," that's tension.

Hughes: Do you think there was less respect for your past achievements than there might have been if you'd moved into an academic job, that the scientists at Genentech were looking at what you were doing in front of them, what you were doing to their science?

Martin: I'm not sure I understand the question.

Hughes: I may be all wrong in this, but my speculation is, if you had moved from UCSF to another academic position, your scientific reputation would have followed you loud and clear. That there would have been a certain respect before you did diddlysquat at the new institution, just because of what you had done. I'm wondering if maybe it's a little different when you go into the corporate world, where it's more, "What are you doing in front of me that is going to—"

Martin: I don't know. I think Genentech was different in that sense. It was more academic-like, or "academoid," if you will. I think it was very smart—and I don't remember whose decision it was—that the first thing I did when I walked through the door at Genentech was to give a research seminar of my own work. It was a very active time in my own lab, because not only had we done some very nice work in immunodeficiency diseases in humans at the molecular level, but we had also just made a transgenic mouse that was expressing growth hormone very early on, by single-cell embryo injection of DNA. I think it convinced them that I was doing, in my own lab, research that was pretty much on the edge. In a somewhat different field than theirs, but we were cloning. We, in fact, had just cloned a human gene in bacteria by expression cloning—which nobody had done before. I think that credibility helped enormously, but it helped, as it would have in an academic institution.

Hughes: Hm-mmm. Right. You either deliberately or just because of the circumstances were being perceived as a scientist rather than an administrator.

Martin: Clearly, I was not an administrator. I hadn't been before, and they knew that. I think that, again, Bob's foresight/insight to hire someone who was a scientist-physician, who had credibility and therefore had a much better chance of being successful leading the research group than he would have with someone who just came in and was appointed vice president of research, who just walked in and said, "Okay, I'm the boss."

I had an interesting experience that is the contrary to that. Years after that I had—this is an involved story, but in effect I was interviewed at Roche and Nutley [New Jersey] for being head of R&D there. I knew Irving Lerner fairly well from an Institute of Medicine

committee he and I sat on. He was the Roche CEO. He invited me to interview, but I didn't want to interview for the job of head of R&D there. I wasn't interested, but I did it out of respect for him. The experience was eye-opening. He was out of town, and I showed up in Nutley in the middle of winter, which is just depressing to begin with, and was invited into the office of the head of human resources, who sat there with a clipboard and a checklist and asked me questions and checked off the answers to the questions. So I thought, "Jesus Christ, what is this?" Then I was escorted upstairs to the top floor, to the office of the person who was head of R&D and whose retirement he had already planned, although I don't think it had been announced. I walked his corner office, about three or four times the size of this room, looking out on Nutley, New Jersey. The office had a white carpet on the floor and a huge mahogany desk and white couches and flowers arranged—it looked like a very expensive hotel lobby.

I sat down and started talking with the head of R&D and during the conversation I asked him, "Tell me, whom else am I going to talk to today?" He said, "Well, Irv's out of town, so there's no one else today, but we'll spend the next couple of hours together." So I asked, "In your recruiting activity, whom else would you have interview me, or vice versa, before you make a decision?" He said, "Oh, Irv and I will make the decision." So, no one else. "Well, suppose you offer me the job and I were to take the job, how would you implement my taking over your position?" He said, "Oh, that's very straightforward. On your first day of work I would gather everyone who was going to report to you in a room. I would introduce you and tell them you're the new boss." [laughs] Oh boy, is this an easy decision! So we talked for an hour or so and then he proceeded to take me to the executive dining room. We were the only people in the executive dining room, and we had two tuxedoed men waiting on us for lunch, and I thought "Oh, God!" To think of moving from Genentech to here would just be the farthest thing I could imagine, and it was not just because it was New Jersey, it was because of this attitude, "The two of us will make the decision and we'll tell everybody else you're the boss." Right? And you have no credibility except your title and the fact we said: Here's the boss. That would have been an absolute disaster. It's interesting that Roche had already announced it was acquiring the majority of Genentech at the time that I was interviewing. The acquisition hadn't been closed, but it was clearly going to close. I learned later that the Nutley organization, the U.S. part of Roche, knew nothing of the Roche acquisition of Genentech until it was publicly announced by the company.

Hughes: So a little bit of compartmentalization.

Martin: Oh yes. I think that the culture Swanson had created within a biotech company and the way the recruiting occurred and the ability to go in as almost a scientific peer of these people who were really smart, driving the company to success, was set up in a way that it was likely to work. In contrast is going into an entity like Roche in Nutley, is a recipe for failure, a disaster in terms of having a scientifically productive organization that wants to work together and follow the leader.

Hughes: And yet, you must have had power in the sense of, for one, allocating resources. Wasn't that largely up to you?

Martin: Sure, prioritization and allocation of resources.

Hughes: You could in essence encourage or discourage certain projects. That's pretty powerful.

Martin: Yes, but I think there was in many cases a complicated—at least, the way I was doing because I was at times shooting myself in the foot. That is, someone would come up with a good idea and I'd listen to it and say, "That's garbage. Forget it. I don't want to hear anything about it." And yet, there might have been value there. And what I was not doing, frequently, if someone had an idea, was to put six or eight really good people in a room and let them listen to the idea, then ask them what they thought of it before I made a decision.

Hughes: I see. So you were making decisions.

Martin: I was so cocksure that I could analyze it and shoot from the hip, that I was screwing things up that way. I know that I did that; I can remember some instances where I did that and I just shouldn't have. Wrong decisions, because I thought I knew the answer and I didn't. On the other hand, when I was trying to convince someone to take on a project, it had to be persuasion. I couldn't go command that they take on the project. I had to sit them down and educate them and get them excited about it, and then they would do it. It was frequently difficult. Obviously, the power and resources helped with the persuasive argument. I remember one instance where Dave Goeddel, who was head of molecular biology, and I were trying to convince Larry Lasky to drop the work he was doing in vaccines—he was working on a herpes vaccine and an HIV vaccine, now is at VaxGen that's failed. We were trying to convince Larry to stop and to go collaborate with Gene Butcher at Stanford working on adhesion factors for lymphocytes and lymph nodes, on selectins that weren't even named at that point. This was probably in end of '86, maybe early '87. Genentech stock was doing really well, just climbing, climbing, climbing. So I remember we had him sitting in my office, and Dave and I were badgering him about how exciting the science was and talked about what he could do. He had met, but didn't particularly like, Gene Butcher, and so he finally said, "All right, all right, I'll do it. It's amazing how much shit you'll eat for a million dollars." [laughs] He had, I think probably within that week, become a millionaire on paper with all his stock options. There was that ability to persuade with resources and to keep your job, but then Larry went on and did a spectacular job on that project.

Hughes: That's what I was going to say. It was not a bad decision on all counts.

Martin: He and Susan Watson did a spectacular job of developing that. It went well beyond what Butcher ever imagined.[1]

Hughes: Interesting. What did you do—very quickly—when you arrived? Anything in particular in terms of reorganization?

Martin: I spent initially most of my time trying to learn what people were doing, nature of the projects. I discovered that I was spending a lot of time passing the project batons, if you would, between various departments to make projects run smoothly and to keep them from being delayed. So for instance, we had a protein biochemistry group, we had a molecular biology group, we had a chemistry group in research. I think those were the three groups. Oh, and we had a mammalian expression group—I guess it was probably part of molecular biology—that was trying to figure out how to express tPA in

1. See the oral history in this series with Lawrence Lasky.

mammalian cells. I decided that spending my time passing batons back and forth was not appropriate, so I reorganized and I established therapeutic-area departments.

We set up a cardiovascular group; an oncology group, an inflammation group. And each of those groups were enough protein biochemists and molecular biologists and cell biologists so that they were more or less self-sufficient in terms of the disciplines and the resources they needed. The departmental head of each group or department could maneuver his or her own resources—it was then "his" only—maneuver his resources as he saw fit on the projects that they were saddled with and didn't have to go beg Goeddel to clone something. And Goeddel didn't have to argue with whoever was doing the expression work that it was a good construction that would express high levels of protein. Because they would always fight about that. "You need to give me a better expression, because I can't get enough protein out of it." Or, "I need more protein than this to sequence so I can clone." All of that sort of disappeared. Yet we still maintained the disciplinary groups, so we had a molecular biology group, a chemistry group, and a protein biochemistry group, we set up a genetics group that was doing the expression. Those discipline groups maintained the quality of the discipline, and yet within the therapeutic-area groups they had resources of all of those skills. We could reinforce the skills within the therapeutic area with these discipline groups. So we created a matrix organization that still exists, as I understand it, and worked much better.

I think as the company became larger before I joined, issues of communication between groups and passing batons within the groups became much more of a problem because each of the departments had developed their own identity and their own silo. They were working on their project, which is usually a technology development rather than project development. I did a similar thing at DuPont Merck; set up a combination of therapeutic areas plus disciplines. Once an organization's big enough to do that, I think it's the right way to go. That was not a trial and error, just a sudden realization that I was spending all my time doing things that I shouldn't be doing.

Hughes: Who were you reporting to or communicating with in the echelon above you? Were you going straight to Bob?

Martin: Right, Bob. I worked for Bob and my peers were Bill Young in manufacturing, Jim Gower in marketing, [Tom] Kiley was head of legal, initially. And then there were the CFOs—there were several CFOS during the time I was there. So that was the management committee, around five or six of us, for several years anyway.

Hughes: Would you go one-to-one to Bob, or was this in sort of a committee setting?

Martin: No. Bob and I met a couple times a week.

Hughes: And how detailed was the information that he wanted to hear?

Martin: He was more interested in what the priorities were and what the progress was and what were we going to do next.

Hughes: And how close you were to the market?

Martin: Yes, just progress reports on projects. What were the issues, what were we not doing that we ought to be doing, and vice versa. He was certainly tapped into a very large community of business people, biotechnology CEOs, et cetera. While I was there he ended up becoming a member of the MIT oversight committee. The members heard science all the time from really good scientists, many of whom were biological scientists. Bob would always report what he heard back to me. He read an enormous amount of mostly lay press stuff and would come up with ideas or questions all the time. So it was a matter of telling him why we weren't doing this or that, or why we shouldn't do this or that, or why we were going to kill this project or why we were going to start that project. That type of thing.

Hughes: And his was the ultimate decision?

Martin: Yes.

Hughes: But did it usually go the way you had suggested?

Martin: Usually, except when there were budgetary constraints, where we wanted to do something and we simply didn't have the resources to do it. Yeah, I think we usually came to an agreement, again by convincing each other. We would have arguments for sure, but they were arguments based on data or logic, usually. Every once in a while he would just say, "Look, I just have a feeling we just need to do this." Not very often. He knew very well with people, that using that approach often would be demotivating. That's something I learned from him, for sure.

Hughes: What about the place of basic research at Genentech while you were there: was there a place for it?

Martin: Oh, definitely. I used to say that the difference between basic research and applied research is about six weeks. That was not so such an exaggeration. A lot of very basic observations could very quickly turn into something that was useful for a product we were making, or an analysis of a target we were pursuing, or a protein, or a clinical trial in some cases. There were a lot of people who were pursuing very basic biology and some of them were particularly good at it. I mean, Axel Ullrich was very good as a biologist, a "molecular oncologist," because he ended up pursuing growth factors and growth factor receptors. Taking a target like HER2 and proceeding on that was something we could attack. Goeddel, on the other hand, was interested in cloning a gene, particularly one that had interesting biological activities, which Gower seemed to have some interest or someone else had some interest because they thought it had commercial viability. So Dave's was a technology thing, that is, to show he could clone more complicated genes faster than anybody else could. That wasn't Axel's thing. Axel wanted to get the growth factors out and understand what they did.

Hughes: Whether or not they had an immediate commercial application?

Martin: But he was still always trying—once he got one out—he was always trying to imagine how they could be commercially viable and trying to convince me that we should put more resources on it.

Hughes: And Swanson could appreciate that long-term goal; there was no problem with continuing?

Martin: As long as we were productive in terms of generating therapeutic candidates, doing the basic research had many advantages. One, it helped with intellectual property, because we could get something very early on from a technology point of view or a target or a molecule point of view. It kept really smart people around. And it motivated. That was perhaps Herb's greatest contribution to Genentech—convincing Bob that what was really critical was having very, very smart, motivated people within the organization, and if we lost them, then the company would not be successful. I think he was absolutely right.

Hughes: If Herb hadn't been there to say that to him, how would his choices have been different?

Martin: The chances are that he would have said, "Look at all the resources that Axel has. And what has he come up with? He hasn't come up with interferon or growth hormone or anything we can make a product out of. All these receptors; we can't make therapeutics out of receptors. So why don't you cut his resources; why don't you put him over here working on human growth hormone?" I had to be careful to balance what Axel had because he always wanted more resources, but he was doing good work. He also was adding greatly, as was the basic research in general, to the reputation of Genentech, which made it easier for us to recruit people.

Hughes: And then, of course, years down the line, look what became of that receptor research.[1]

Martin: That's right.

Hughes: Let me just see. I know you have to go; I just want to get through this one section. Okay, one last question for now. You may have answered this indirectly, but I'll ask it anyway. You were there primarily to deal with the science and the scientists, but how often did it happen that you had to let the scientific side of it, to a certain extent, go—maybe even in terms of your own interest—because of business prerogatives?

Martin: I certainly let what was going on in my lab, the whole interest in gene therapy, expire with the expiration of the grant support. I got my lab onto other things, and I was using my lab mostly for some way out things—"way out" in terms of high risk—but if they worked they would be useful. I could do that with a couple of technicians and a scientist.

I can remember the one area that I tried very hard to get going, and it was really difficult for financial/business reasons, is that with all of the receptors that Axel was leading the cloning and expressing it was so apparent that we needed a small molecule effort to screen for agonist and antagonist against those receptors, because we knew they had biological activity. My feeling was that it was a great opportunity to go beyond the aortic strip and a smoke drum for screening for active drugs. We could actually screen for binding or function with these cloned receptors where we had them in pure form, and we could really understand exactly what a small molecule was doing. So I got

1. See the oral history in this series with Axel Ullrich.

Bob's commitment to build a small molecule group and recruit chemists. We were going to try to get a jump on all the pharmaceutical companies, because I figured they were all going to go that way. This was back in about '84, '85. I remember Bob introduced me to Paul Janssen of Janssen Pharmaceuticals who had this big high-throughput screening system looking at all sorts of molecules. They were using, in effect, smoke drums and aortic strips. I talked to Paul on the phone about the fact that we had these cloned receptors and we could get pure receptors. We could get all the ones he didn't want to react with and all the ones he did want to react with. He had no use for it whatsoever. I think that was something that didn't help my cause, but the biggest problem ended up being financial. We started to build a chemistry group, hired a few chemists, and we had plans to recruit sixty chemists. But tPA never took off the way we had projected it would in terms of revenues. Hence, we had to pull back and that's where we pulled back, because we hadn't built it yet.

So the small-molecule effort at Genentech sort of limped on for years without ever more than about eight or ten chemists, which is just not a critical mass. They got a couple of small molecules—peptide mimetics—out of it and an integrin antagonist, but that was one opportunity that I think Genentech really missed for financial/business reasons. But had we developed the effort, Genentech would be an even bigger company than it is today—they'd have all the pharmaceutical chemistry to go with it. It would have been light years in front of everybody at that time.

Hughes: Everybody, meaning biotech and big pharma?

Martin: Big pharma use pretty much all cloned targets now. But that was a strength we had and we were in the lead, and it was a matter of how do we capitalize on this strength, take the next step? Can't do everything.

Hughes: We better stop there.

[End Tape 4, side B]

Interview 3: March 3, 2004
[Tape 5, side A]

Hughes: As I just said, we got into Genentech last time. Let's carry that conversation a little bit further. When you arrived, was there an overall research strategy in place? What did you find?

Martin: Well, there was a major emphasis within Research on cloning various biologically active molecules that in general were known to be active in some type of *in vitro* assay, rather than necessarily active in humans. By the time I got there, human growth hormone had already been in a couple of humans, mostly volunteers from Genentech. They all became sick because it had plenty of endotoxin in it, so they were very sore. So growth hormone was then on its way into development in humans. tPA had been cloned just before I went there. There was a lot of effort on gamma interferon, TNF [tumor necrosis factor], lymphotoxin, all in the first period of months that I was there.

The place was divided into various disciplinary departments. There were departments of chemistry protein biochemistry department a molecular biology a pharmacology. The research process was an awkward one at this stage. Genentech had grown beyond just a small research activity. As a result, the communications and interaction between the various departments was not spontaneous and easy, because they were all working in the same lab or few labs. I found myself spending much time facilitating the passing of batons between the departments. The process was to purify certain molecules in protein biochemistry and then sequence their amino acids, then the chemistry group would make specific, oligonucleotide probes, to try to clone these molecules, molecular biology would clone the corresponding cDNA from libraries and then make the protein, protein biochemistry would purify it. Each time the baton passed between departments, it was a problem because the receiver always had other priorities. We ended up having to reorganize the research group into what we referred to as "therapeutic area" departments. Each department had the skills needed and could operate with a common goal priority and priority—that is, to purify various protein, clone and express the cDNA and make enough of a given molecule to assay biological activity. We maintained two smaller disciplinary departments, oligonucleotide chemistry and molecular biology. Later we added genetics department.

Hughes: That was a separate department?

Martin: We had several therapeutic area departments. One was pursuing cardiovascular projects, one immunologic projects, one endocrinologic projects, et cetera. That certainly started working much better. That was something we had to do within about my first six months.

Hughes: Was that your idea?

Martin: It was my solution to the problem I saw, that I was just spending my time in the wrong way. Then there were other issues that had to be addressed; many of them were the result of a small company suddenly becoming large. At the time I joined Genentech, I think that there were at least two hundred people in R&D, and the entire company

employed about four hundred people. Manufacturing was across the street, and that was another issue that had to be addressed. All of the fermenters that were used for making proteins in any quantity in bacteria were all under the auspices of Manufacturing, and they always had other priorities for their fermenters and their time. That ended up creating a polarization within the organization—that is, between R&D and manufacturing—which was totally unnecessary.

Hughes: Was it more than a difference in scale? Moving from the test tube—

Martin: It was a difference in attitude, not just scale. We had no fermenters in research and the people in manufacturing didn't want us to have fermenters; they wanted control of the fermenters. There were so many growing pains of that sort that I found myself trying to address, pains that I never anticipated coming out of academe.

Hughes: Right. Am I right in thinking that growth hormone was the first thing that Genentech had really developed? Is that not the case?

Martin: Yes, on its own. Human insulin—However—

Hughes: Was a Lilly—

Martin: —was licensed to Lilly to develop, right. As Irv Johnson transferred.

Hughes: Yes. So these problems were really very fresh when you arrived in 1983, because growth hormone was not approved, as I remember, until 1985.

Martin: Yes, I think that's right—'85 or '86.

Hughes: And it was slow. Do you remember that? It was an expectation on Genentech's part that FDA [Food and Drug Administration] approval was going to come sooner than it actually did.

Martin: Absolutely. There was an FDA medical reviewer in what is now CDER [Center for Drug Evaluation and Research]—who had the primary responsibility for reviewing growth hormone. He was a pediatrician. He was a serious problem for the FDA as well as for us. He was on a power trip and was having a wonderful time jerking around Genentech, asking us to do things that we felt were unnecessary, inappropriate, and, in effect, unethical. For example, we were having some problems with antibodies to growth hormone, and the only pre-clinical assay that was seemed to predict whether a prep was going to generate antibodies in a patient was to administer it to chimps. So we were conducting studies in chimps, and then he started insisting that we sacrifice the chimps to look at their kidneys. Unfortunately, it's one of those situations where you're at the mercy of a medical reviewer in the FDA. We argued with him and he stonewalled us. So for no good reason other than his power drive, we had to go through a study and then kill a series of chimps to look at their kidneys. There were so many other ways of doing the same study without sacrificing animals. We ended up with that problem. Then, as they kept stalling the approval and coming back and asking more and more questions about growth hormone—particularly the medical reviewer.

Hughes: [laughs] The name is still a memory.

Martin: We even hired a psychologist to profile him so we could try to understand what was motivating him; he was so bad. He eventually was fired or pushed out from the FDA.

Hughes: Excuse me for interrupting, but had he been chosen because he was a pediatrician and consequently would be the one most likely to be treating children with growth problems.

Martin: I don't know.

Hughes: You think his specialty was incidental?

Martin: It probably was relevant, but I'm not certain that was the primary reason. I just don't know. But what happened subsequently were actually quite interesting. The growth hormone being provided and children with growth hormone deficiencies was under an IND [Investigational New Drug] that the NIH had had open for more than twenty years. They were providing human growth hormone free, and they had contracted with a supplier who was purifying it from pituitaries of cadavers and then supplying it to NIH. NIH would distribute it to physicians who were using it under the open IND. It became apparent that the sources of these cadavers were uncontrolled. I and some others became concerned that the cadavers were from countries where the causes of death where unknown and where there were some serious, what we called, "slow virus diseases," which are now known as prion diseases. We didn't know about prions at the time. I actually wrote a letter twice to the FDA suggesting to them that they should monitor the sourcing of pituitaries if they were going to continue to distribute growth hormone from cadaver pituitaries, in fear that some of the people who were receiving growth hormone would end up with slow viral diseases such as CJD.

Hughes: And didn't that happen?

Martin: It happened. I never got a response from FDA. I wrote also the physician at NIH who was managing the IND, but I never got a response from him either. However, about four or five months after that there suddenly appeared in the UK a couple of young adults who had Creutzfeldt-Jakob Disease, and it was on the coattails of that that we acquired an approval for recombinant human growth hormone. That's the only reason it happened, and the medical reviewer at the FDA was essentially forced by those pressures to approve it; it had been shown to be safe. We knew that we had antibodies, but the antibodies had never compromised any growth in a patient, with one potential exception that was never proven. That was the first product that Genentech had approved. It's quite interesting in the context now of BSE [bovine spongiform encephalitis], Creutzfeldt-Jakob Disease, and prion diseases. It was essentially the same thing, a prion disease causing Creutzfeldt-Jakob Disease where the source was the cadaver pituitary growth hormone that was being injected. That was certainly one thing that recombinant DNA technology could prevent—was a pure product.

Hughes: So a tragedy had a silver lining.

Martin: That's right.

Hughes: There must have been a learning curve, however, on Genentech's side, above and beyond the difficult pediatrician. I'm imagining that it is important to present data in a

certain format to the FDA. Were there people on board at Genentech who knew how to do that kind of thing?

Martin: Sure, there were. We had a regulatory group that was run by Sandy Ronspies, who had experience. It was a small group and we all pitched in, but yes, we had professionals that dealt with regulatory issues. Essentially no one in research had any prior exposure to the FDA. I had once filed a physician-sponsored IND, that was it, but Sandy educated us. We were adamant about presenting high-quality science and lots of data to the agency. There were issues. With the tPA approval there were a couple of very serious hiccups that we eventually overcame. As always, there were personalities involved. We had a medical director at Genentech who loved to debate, so he wanted to go to the FDA advisory committee meetings and debate with the members of the advisory committee. We got shot down once based on this practice and then finally recovered by going to the commissioner directly.

Hughes: The debate implying—?

Martin: That they were stupid and he was smarter, so they nailed us. Frank Young was commissioner and we secured an approval about three months later, after presenting a bit more data. The data were from an Australian study that showed a beneficial endpoint, which was the ejection fraction. The FDA would not accept—that was wrong, and is certainly wrong today—that clearing a blood clot out of a coronary artery was of benefit to the patient. They wanted to have us show some other benefit and so we showed as a benefit improved ejection fractions in a patient in a small series of patients.

Hughes: What does that mean?

Martin: It means that after a heart attack the heart worked more effectively if the patient received tPA. The ejection fraction is the measure of how much blood in the heart is actually ejected upon each contraction. They finally accepted the study of about thirty patients in Australia. That was the endpoint. They said, "Okay. That will benefit the patient. We'll approve the product."

Hughes: But why wasn't it sufficient just to have the clot dissolved?

Martin: Because the FDA is very adamant—and perhaps even at times pathologically so—about proving an unequivocal benefit to the patient. They said, "Just because you dissolve the blood clot, maybe it's too late and the damage has already been done. So how do we know that's good? Maybe it's bad. Show us that it's good." So we had to find another endpoint. We assumed that if you dissolved a clot in the coronary artery that's good. That's not always been known, because it wasn't until maybe 1950 that it was clear what a heart attack was, that it actually was a clot in the coronary artery. But that was proven beyond any reasonable doubt, so we thought, "Well, if that's what's causing it and you get rid of it, it's good." They said, "Well, it may not be good."

Hughes: Could streptokinase have been part of their thinking? Doesn't streptokinase dissolve a clot?

Martin: Does the same thing; sure.

Hughes: So could it have been, "Why should we approve tPA? We've got streptokinase and it's doing the same thing."

Martin: The FDA will take that position at times; that is, that they don't want to take any risk of approving a product if the medical need is satisfied already. They'd rather have evidence beyond any reasonable doubt that a product candidate is both safe and efficacious. Whereas in certain diseases—I mean, certainly the AIDS lobby had a major impact—they eventually are willing to accept surrogate endpoints. This whole thing was a surrogate endpoint argument. With growth hormone, we just measured growth rate, and that presumably was indicative and a child who was growing too slowly was going to be really short would grow more rapidly and ultimately become taller.

Hughes: What was the timing of that? Had AIDS, with the surrogate endpoints, already been established?

Martin: No, no, no. AIDS was out there. Surrogate endpoints came much later. Surrogate endpoints for AIDS therapy came probably in the nineties.

Hughes: I think you're right. Because the epidemic was certainly out there, but not the drugs to treat it. That was another thing that happened then. I mean, that's quite significant, is it not? It seems to me significant that the FDA developed a new set of criteria for efficacy.

Martin: Right. I think because Frank Young wanted to approve it, wanted to have the feather in his hat for having approved a new technology-based therapeutic, he convinced his medical reviewers to give a bit, give us an efficacy endpoint based on the ejection fraction.

There was another interesting lesson in there that Genentech learned, and I know that certain academics learned. One of our clinical consultants, a well-known cardiologist who was working for our marketing department, was trying to help us get this drug approved. Marketing—which was being run by Jim Gower at the time—had granted this cardiologist a lot of Genentech stock options. In the meeting with Frank Young, which was in June of '87, the cardiologist, Bob Swanson, and a couple of other people marched into Frank Young's office—Gower and I were outside—and sat down to convince him that tPA had to be approved. The cardiologist never acknowledged that he had a very large interest in Genentech stock options. The drug was approved and someone in the press picked up on that a conflict of interest few months later. He was accused of having a conflict of interest that wasn't disclosed, and he lost a lot of face in academe. He left a major university and went to a small academic center. He seemed to disappear into the sunset because of that ethical issue. Genentech took some heat for it, and I think we learned—at least, the marketing people learned—that you couldn't give someone a bunch of stock options and then ask them to go persuade a regulator without disclosing their conflict. I think a number of academics very quickly learned, "Don't take options. Or if you do, don't ever obscure the fact that you have them." That, to me, was sort of the beginning of this whole issue of disclosing your vested interest in the outcome of a study, which now all journals are requiring. I think that was the first really blatant example of abuse that I know of.

Hughes: It sounds as though it's never a straight science or regulatory issue. Certainly, there was that tussle between streptokinase and tPA and the GUSTO [Global Utilization of

Streptokinase and tPA for Occluded Coronary Arteries] trial and all that. Was that during your tenure?

Martin: Yes. That was all in the eighties. There were some other studies. There were several GUSTO trials—III, IV, V, VI, et cetera—so the early ones were during my tenure.

Hughes: How would you summarize the outcome of those trials?

Martin: I guess my assessment was that, initially, tPA was shown to be superior streptokinase by a measurable and statistically significant margin but then on subsequent studies it was questionable just how much better it was on first-time use. I think the other issue was changing the dosing regimen, which we ended up doing, so it was more rapid dissolution of the clot by increasing the front-end loading amount. I can remember having very intensive discussions with Gene Bramwell and several other cardiologists about how we ought to be dosing tPA in order to optimistic the dosing regimen. We also started a research program trying to improve tPA so it would act faster, that's engineering a better product. That was another activity started in the late eighties. That's now this fast-acting tPA which is on the market; tNK.

Hughes: Would that have gone back to the scientists, to do that?

Martin: Oh, absolutely. We set up a large multidisciplinary project team.

Hughes: Would there have been the tensions that did evolve around the GUSTO trials if there hadn't been such a huge price differential between streptokinase and tPA? Wasn't it tenfold, something quite significant?

Martin: I think it was about tenfold, two hundred versus two thousand—an order of magnitude. That certainly fueled the fire. I can remember having a discussion [laughs] with Ernest Gallo about the time that tPA was approved. As a member of the advisory committee of the Gallo Center [at UCSF] I had dinner with him one night a day or so after approval. He said to me, "Well, you just got tPA approved, but why in the world would anybody want to use it, because you can get exactly the same thing for less than two hundred dollars? Why would I want to pay two thousand dollars?" I said to him, "Well, if it were me, I would take the tPA. You might take the streptokinase." He said, "Of course, I would." I said, "Well, you should ask your physician what he or she would want you to take." He said, "But I'll <u>tell</u> my physician what I want to take." It was so interesting that Gallo at that time was making at best a mediocre table wine. Ernest had an old Cadillac, not quite old enough to be an antique, but the reason was that he didn't like to spend money. He would wear what always looked to me like J.C. Penney suits. So here's a billionaire who's really tight, who's telling me he wouldn't use tPA, he'd tell his physician to use streptokinase because of cost.

Hughes: And maybe jeopardizing life.

Martin: Perhaps. That same night I sat next to their CFO [Chief Financial Officer] at dinner. They always would take us to a nice restaurant and bring Gallo wine, and so there was a bottle of wine on the table. I asked Lou Friedman, the CFO, about the bottle of wine and he said, "That's really one of our best. That's a family reserve wine." It was a chardonnay, as I recall. I said, "Oh, really?" He said, "Top of the line," and I said, "Is it

available? Can I buy it in a liquor store?" He said, "Well, you might be able to find it in one or two stores in the City." This was late eighties, ate '87 or something of that sort. So I said "Oh really? How much would I have to pay for it?" He said, "Well, it's really expensive." I said, "How much would I have to pay for it?" He said, "You'd probably have to pay $7.50, $8.00 for it." [laughs]

Hughes: So that's his standard.

Martin: So this whole tPA/streptokinase price differential is—I believe there is a quality difference, but then there's always an issue whether it's worth the price differential. I think one of the things about streptokinase, and this is true in general in the pharmaceutical industry, is that unless you market a drug, it won't be used. The profit margin on streptokinase was so low that no company wanted to spend the money to market it. So it was passively marketed, whereas tPA, there was a good margin, Genentech would market this it was used more. It goes beyond science very quickly.

Hughes: In both projects that you've discussed today, Genentech had a lot riding, aside from just getting drugs on the market, because—and I want <u>your</u> views on this—my understanding is that Swanson from the very start wanted Genentech to become a fully integrated company. Would you say that growth hormone got it there?

Martin: Sure, because when it was approved that was the first time we had a product to sell with our own sales force, whereas with Lilly selling insulin, we didn't need a sales force. We couldn't have sold it, far too big a sales force was required for insulin. But for growth hormone, I thought it was a clever strategy. For growth hormone, it only took a small hospital-based sales force because it was only hospital-based pediatricians, mostly academic pediatricians were seeing these small kids. They were mostly in tertiary medical centers. It's expanded since then. But that was the strategy to beome a FBCO [fully integrated biotechnology company].

Hughes: Was everybody in place by the time you arrived? Pretty much. I mean the marketing strategy?

Martin: There was a marketing group, but they didn't have any sales people. They had a couple of marketing people.

Hughes: So that was quite a change. That must have gone a long way to explaining the increase in size, right? From a research boutique—which it had been, would you say—through human insulin, it was now on its way to becoming a pharmaceutical company? Can you go that far?

Martin: Yes, I think it was. I think the transition point was when, before I was there, they started building the manufacturing facility across the street. One doesn't build a manufacturing facility unless a product is going to be approved. That was the transition. The people who were in marketing had been doing business development, primarily, and then evolved into a marketing group. Gower, I think, was originally in business development. There was another executive heading business development just as I came in who left, and then Jim was promoted to head of business development and became head of marketing.

Hughes: From some of the conversations I've had with the very early scientists, I've come away with the idea that there was rivalry among—

[Tape 5, side B]

—divisions, or whatever you want to call them. I would think that you as research director would have had to have dealt with some of it. Maybe that was kind of in your mind when you were talking about "passing the baton." Could you expand on that a little?

Martin: At the time, in the late seventies and early eighties, molecular biology was coming into another era where one could use recombinant technology to do real molecular biology. That is, gene-jockeying molecular biology. It seemed that everyone wanted to be a molecular biologist, including a lot of people that had not started out that way for sure. In academe there was no real molecular biology training back in the sixties or seventies. A biological scientist was trained as a protein biochemist, an enzymologist, a geneticist, or a pharmacologist, for example. Then the tools became available and people started deploying the tools. Not long afterwards, universities started granting degrees in molecular biology, PhDs in molecular biology. Because molecular biology was the hot field, the molecular biologists migrated to the top of the pecking order in most people's perceptions within and outside of Genentech. So in pecking order, the molecular biologists were dominant, just in general. There were personality issues that came to bear on that, obviously. Some of it was selection; some of it was induction. But there was molecular biology and then there was chemistry, and then there was protein biochemistry, and genetics, et cetera. I would guess that it was probably molecular biology and then genetics and then protein biochemistry. The chemistry group we had there was very small, and it was specifically to make synthetic DNA. That was its only chemistry function at the time.

There were some forceful personalities in there. Dave Goeddel was head of molecular biology. He's a very forceful, very competitive person. During the time I was there, there were two or three heads of protein biochemistry, and in general they were older, more mature people, because they'd been trained maybe ten years before. Because of the popularity of molecular biology in the eighties no one coming right out of graduate school at that time had a PhD degree in protein biochemistry. They all wanted to become molecular biologists. So we had a hard time finding protein biochemists. Most of the geneticists had very quickly become molecular biologists. Most of the protein biochemists or enzymologists had just moved into molecular biology. They were very good molecular biologists because they understood proteins and biochemistry and enzymology. There was that pecking order, and that was one of the problems with baton-passing. That's when we created the multidisciplinary departments and then put a person in charge of each department who had at his—and it was primarily a male-dominated culture, if you will—had at his disposal the skills that he needed to coordinate a project. He didn't have to argue with different departmental chairpersons to get his project done. It was the evolution of technology that is nowadays frequently led by industry and followed by academe. Academe now trains people to do these different industrial jobs.

Hughes: You alluded to a number of projects, and I have also heard that tPA began to more and more dominate the agenda, at least from the feeling of some of the scientists I've talked to. Other projects, which they felt were promising—the vaccine program, for example, is one that has been mentioned specifically—were demoted, and resources prioritized for tPA. Were you involved in that kind of reorientation of effort?

Martin: Yes, tPA was taking priority in development, but by the time I arrived at Genentech, tPA had already been cloned and was being expressed. It had been cloned in the early fall of '82. In research there were other projects that were taking more precedence at that time, and those were the TNFs and lymphotoxin. Gamma interferon had a big effort going on in late '82, early '83. In fact, erythropoietin was presented, I think to Gower, just before I got there early in '82 as a project by a scientist, Greewald at the University of Illinois, as I recall—who claimed to have purified erythropoietin. I don't know why Gower made the decision; at the time there was not a head of research or R&D, so I guess it fell upon him to decide whether it was of interest commercially. He turned it down apparently because he said that gamma interferon was going to be a much bigger product and Genentech had all its resources forward on gamma interferon. At that time, gamma interferon was touted to be the cure for cancer, primarily.

Hughes: Right. I remember the hype.

Martin: Not long after I got there, within a month or so, I guess this was probably April or May of '83, erythropoietin came back through the door with a scientist—who claimed to have purified it and showed me her material, the scientist was from New York, as I recall. We knew that Amgen was already working on it and there were some patent issues coming from Illinois. I decided not to take it up at that point because we were behind the patent issue and what she showed was very far from pure—I didn't believe it. The gels just didn't show what we would need: a protein pure enough to sequence. The only way to clone it at that time was to sequence the amino acids and probe a library with a degenerate oligonucleotide. So we let that one go. GCSF also [granulocytic cell stimulating factor] showed up, I think also not when I was there, but during the gamma interferon effort, and that was turned down. I don't recall whether that was Gower or someone else. But it was interesting in terms of which projects were dominating the scene. Gamma played, I think, a much bigger role in research than tPA. When it came to development, tPA played a very big role because it was a very expensive study to conduct as a cardiology study on a bunch of patients. It required a lot of money but the expectations were that that would be a billion-dollar product. The projection, as I recall, was four hundred million in revenues for the first year.

Hughes: [laughs] And what were they?

Martin: I think it maybe hit seventy-five, eighty, something of that sort.

Hughes: What went wrong there?

Martin: Market research rarely, if ever, is accurate. Or rarely, if ever, can predict the outcome, because of the way market research is done. Growth hormone was predicted to be a ten-million-dollar market. It's currently a billion-dollar market, so they were a hundred-fold off there. I have very little faith in market research, for that reason—particularly for anything new. The way the analyses are done is market research people go out and look

for an example or a prototype for the product they're trying to assess the market of. If there's nothing there, they can't do it. If there's something there, they'll just pick that number and say that's a certain fraction of the market. It just doesn't work. The people in marketing believe in market research. I think that's a big mistake.

Hughes: I think it's interesting that Jim Gower—in both those cases?

Martin: I wasn't there, but I am told that Jim Gower turned down erythropoietin.

Hughes: But he's not a scientist; what was his position?

Martin: Marketing. Head of marketing.

Hughes: As an outsider, that strikes me as an interesting decision. [laughs]

Martin: Yes. In a small company, everyone participates in decisions, and certainly if you're going to work on a project you need to know that there's a market there when you get approval.

Hughes: Yes. I can see that, but I would think that would be only part of the consideration.

Martin: Particularly if there was nothing in the market which allows one to assess how big the market's going to be, and erythropoietin wasn't there. About that time, in fact—in fact, it was at exactly the same time—I was in Washington at clinical meetings and had dinner with a good friend of mine who was a nephrologist. He was at Emory [University] at the time. I think he still is. I asked him what fraction of renal failure patients he thought who had anemias, would respond to erythropoietin. He was actually a very smart guy, a researcher and physician, and his comment was "Oh, I don't know, maybe a half or a third of them would respond." That's the point, when you start doing what we used to call "grandmother surveys," you just go ask your grandmother what she thinks of this market opportunity. There was a great underestimate of the market for erythropoietin because the market did not pre-exist. No one had ever tried it, didn't know how efficacious it was going to be, didn't even know how much it was going to require for dosing. What really makes the market is not renal failure patients, it's chemotherapy patients. Huge market. No one was thinking of that at the time, except maybe Amgen. We certainly were not thinking of it. So the influence of market research on project selection is highly precarious, highly unreliable. I've seen that certainly in the biotech industry. I've also seen it in the pharmaceutical industry, although they make fewer mistakes that way just because they've been burned before, whereas those in biotech usually haven't. It's a significant issue in terms of what project on let's dominate the consumption of resources.

Hughes: And one that I imagine that you had to tussle with. Didn't you look at yourself as representing the science?

Martin: Oh yes. Sure.

Hughes: Consequently, I can imagine that there are some tensions when business decisions dominate.

Martin: Absolutely. I think that one of the probably clearest advantages of being a physician in that position is that, for many diseases, I had a pretty good feeling or I could quickly get a feeling for whether there was a medical need or not, or how likely something would be useful. It gave me a certain credibility in my arguments about why this was a good project and that wasn't. The major advantage is to be able to say, "And this is why this is a good project." It's hard to shoot things down and say, "Oh no, that's a lousy project. I wouldn't do that," because there are sort of disrupters that occur. For example, Genzyme was working on Ceridase, the enzyme missing in Gauchet's disease. The number of patients is very, very small. I can remember Bob Swanson asking me one time what I thought about that, because he knew that Genzyme was starting to work on it. They had come and asked Genentech to collaborate with them. Genzyme was using naturally purified material rather than recombinant material, and they wanted some molecular biology help, which they didn't have. My assessment was, the market's just too small to go after it. Well, if you charge a hundred thousand dollars a year per patient, that's a disrupter. I was thinking, well, you could charge ten thousand. If you had ten times more patients, it would be a good niche market. So one was completely thrown off by those things. Being a physician helps to a point. But on another point one can still make big mistakes.

Hughes: Who were you having to argue with? Or "convince" maybe is a better word to use. Who was at meetings, or was it a changing panoply? I guess I'm asking for how were decisions made, and under what circumstances?

Martin: Most of the time it was convincing Bob. If Bob was not convinced, and if we collectively couldn't come up with good arguments as to why a project should be pursued, he wouldn't be convinced. While one might be able to start the project, the chances are when the going got tough or resources became constrained, one would just be forced to cut it. So the real trick was don't start them if you thought they weren't going to be supported. If you could get them to an inflection point in the evidence you had that it was going to be a good project, then it was fine. You could go chase that inflection point. But you had to know that if you started out with not a lot of support, there was something you could achieve in order to increase that support. So you had to target that initially.

Hughes: Does the situation with monoclonals enter into this particular discussion?

Martin: It did with HER2.

Hughes: But even before HER2, or am I not right in thinking that?

Martin: Well, there was the anti-T-cell antigen that Ortho had. Anti-T3. The first one that was approved. That was out there; it was a mouse antibody.

Hughes: When would that have been?

Martin: Seventies, it was approved.

Hughes: That early?

Martin: Yes, it was very early. It could have been ‘80, but it was certainly out there before I left academe, because I can remember talking with Gideon Goldstein—who had done that project for Ortho—about it. They were getting a lot of HAMA responses, or human anti-mouse antibody responses.

Hughes: Was that the first monoclonal-based therapeutic?

Martin: Right, that was the first one. Then it was damn near twenty years before there was another one approved, because of the anti-mouse response.

Hughes: Does that explain why the initial effort—I mean, this comes mainly from talking with Herb Heyneker, who as you probably know was quite enamored of the potential of monoclonals.

Martin: Yes, but now he’s enamored with the potential of polyclonals.

Hughes: Oh, is he?

Martin: I know Herb well. I skied with him the weekend before last in Deer Valley.

Hughes: He felt that Genentech was not supportive in those early years. He was working on monoclonals in the early eighties as I remember. He had to have been, because he left for Genencor in 1984.

Martin: The two key Genentech patents that most everyone in monoclonals infringes were from Herb’s lab. He was working on them with Art Riggs—

Hughes: That’s the Cabilly?

Martin: Cabilly, yes. Cabilly was a postdoc of City of Hope with Art Riggs. There are two, Cabilly 1 and Cabilly 2 patents. They were trying to make recombinant antibodies in *E. coli* and they got a little bit. We filed a patent on it. I can remember sitting in a meeting, trying to decide whether to file the patent on it or not. We did, fortunately for Genentech, because they make a lot of money on it, still do. But the whole issue of humanizing, or using human antibodies, was not yet resolved in terms of how to do it. The first serious effort at Genentech was the anti-HER2 antibody. That was up and down and around. It started up, was killed again; started up and was killed; clinical trials finally got started, just as I left. They got off on the wrong foot in the clinic and had to retrack.

Hughes: Was it completely humanized at that point?

Martin: It was pretty well humanized at that point.

Hughes: Because that was the barrier, wasn’t it? The real barrier.

Martin: Yes, that was the real barrier. There was also concerns about the dose and cost of anti-HER-20. The reason that more people didn’t jump into monoclonals in the seventies and eighties was the HAMA response. Once the humanization process was there, it made a big difference.

Hughes: Boy, and now look what's happening.

Martin: Absolutely. Genentech's has a huge antibody portfolio. Against many sorts of targets. It's a good technology.

Hughes: Okay. Let's see where we are.

Martin: In fact, let me just comment on the vaccine. The vaccine is a complicated issue that I spent a lot of time thinking about then and since. One of the things that happened shortly after I joined Genentech was that Genentech issued a press release saying that Genentech had no interest on working on a malarial vaccine because there was no market for it, which is true in the developed world. Genentech took a lot of flak about not being interested in undeveloped markets and malaria that kills two million people a year. But yet we had a vaccine development department. Before I was there, Genentech had a hepatitis B vaccine project. Merck wanted to acquire that but Genentech's asking price was too high, so Merck walked away and licensed the Chiron hepatitis B vaccine. Genentech's hepatitis B vaccine was eventually sold to SmithKline for their Belgian company, RIT.

Hughes: Were those two vaccines essentially the same?

Martin: Similar. Very similar.

Hughes: They were both yeast-based?

Martin: [pauses] I don't remember—no, ours was mammalian-cell based.

Hughes: Would that have given any advantage?

Martin: I doubt it. They both had patents, and I don't know whether Merck and RIT cross-licensed or not, but they both have legitimate products out there. The hepatitis B vaccine is the biggest-selling vaccine in the world. That's greater than a billion-dollar product, but at the time no one thought that vaccines could be that large in terms of revenue generation.

Hughes: Last I heard hep B was the most lucrative patent at UCSF, even surpassing Cohen-Boyer.

Martin: Could be. I don't know.

Hughes: But very lucrative. Of course, the Cohen-Boyer is split between Stanford and UC. Probably the total income from Cohen-Boyer is greater. I'm only guessing.

Martin: Probably. It's a big product. But then, the other issue around vaccines was the tort law, the product liability issues that we and every other pharmaceutical company or biotechnology company has been concerned about. Unless you can make a significant profit out of it, it's not worth taking the risk. In spite of the fact that particularly for subunit vaccines, recombinant technology really works and certainly makes a much safer vaccine than one can make with a whole-cell vaccine, like whooping cough vaccine—pertussis, et cetera.

There was a real push within the research organization and I certainly supported it, to develop subunit vaccines, including trying to make the HIV vaccine, gp120. There was a lot of resistance against doing that, from a marketing point of view, because of the product liability, and the concern about there not being a market vaccine. The herpes vaccine was another big project, all being carried out in a small group including Jack Obijeski, Larry Lasky, Dan Yamsura, and Phil Berman. I can remember that on the HIV vaccine we met with Jonas Salk several times, trying to get him to use his influence at the World Health Organization to issue a purchase order to us. We don't want to be involved in a market failure. We said, "So just get WHO to put a five million dollar purchase order in front of us for an HIV vaccine, and we'll put real resources on it." He tried and couldn't do it, so then he started his own company, [The] Immune Response [Corporation]. There was some very nice work that went on in the late eighties that mostly Phil Berman did. We pulled Larry Lasky off of it. It was very nice work, but it simply didn't make a valid vaccine, and as you know, Genentech spun out VaxGen a few years ago.

Hughes: Right. That was after you left?

Martin: Yes. They were beating a dead horse at that time. That reminds me of another interesting time, which was in the late eighties, maybe '87, '88. We had an HIV vaccine program, and we had the CD4-IgG program, which was to fuse one of the cellular receptors for HIV—to the heavy chain of an antibody, so that it would circulate for a long period of time and try to soak up the virus. We had that project on-going, and there was a lot of money available for AIDS research at the time, as well as a lot of interest out there.

Hughes: This is late eighties?

Martin: Late eighties. Shortly after the virus was discovered, which was what, '85 or '86, its receptor, CD4, was defined.

Hughes: In '84, I think. Depends on who you were paying attention to.

Martin: Exactly! So I came up with a modest proposal that we spin out a company, put all of our HIV projects into that company—the CD4 project, the HIV vaccine project—and that we go seek government funding from SBIRs [Small Business Innovation Research], that Genentech put in a bit of money and all of its IP, and then we'd go acquire venture capital funding. We were going to wind it down within our research organization, but I felt that if we spun it out we could fund it, keep the thing going, and maybe they'd eventually be successful. It had one other component, which was the killer that would have made the difference. That was that Bob Swanson should go run this start-up, because he was so good at doing that, and the company at that time was getting to the point that he was not good at or really interested, it seemed, managing a fully integrated company.

Hughes: And Raab was on board.

Martin: And Kirk was there, trying to market products, and they weren't getting along. I figured that this was the right solution—to give Bob something that he really does well and let him make something out of it. Merck and Boehringer Ingelheim were both very

interested in the HIV vaccine. I presented it. I went to [Thomas J.] Perkins, Herb [Boyer], and Kirk thought it was great. Everybody thought it was great, except Bob. [laughs] He wanted no part of it.

Hughes: And why was that?

Martin: He didn't want to give up the mother ship. My proposal was to put him out in a whaler and let him go do it. He'd proven his ability to do it, and he could have raised all the money he wanted. It ended up that neither one of those particular product candidates survived. They weren't efficacious, but if the funding had been there and he had been running it, they would have come up with something else, maybe a small molecule protease; protease inhibitor was known at that time. So the whole thing could have been there; it could have been the AIDS company. I think if Bob had done it and he had put that group of HIV interested scientists in there—there were some really good scientists working on it—it would have made a difference.

[Tape 6, side A]

Martin: Many years later VaxGen was formed with Genentech backing, Don Francis being the CEO, and Phil Berman as CSO. They had credibility and they raised money [for VaxGen]. And they continued to raise money. There are people who are always hopeful. I have a lot of respect for Don and Phil, but they were too emotionally involved to make objective decisions about when to kill a project. That's not unheard of.

Hughes: Right. And it becomes, you kill a project in that case and you're killing a company. I mean, if you get to the stage where you've founded the company—

Martin: Spent all your money and you have nothing to show for it. That's right.

Hughes: I read that you made a statement, at least one congressional hearing about continuing Genentech's AIDS vaccine program.

Martin: No.

Hughes: What I have is: "Dave Martin represented Genentech at a congressional hearing in January '87 and asked the government for assurance regarding a potential market for an AIDS vaccine, i.e. would the government buy in bulk?"[1]

Martin: I did not testify at a congressional hearing. I was convinced, mostly by non-scientific management, that if we had a purchase order or someone would commit to buying our vaccine if we could make it, then that would define the medical need and the market viability.

Hughes: Were you able to continue <u>your</u> research at Genentech?

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1. Interviewer's notes on Jon Cohen, *Shots in the Dark: The Wayward Search for an AIDS Vaccine*, W.W. Norton, 2001, p. 72.

Martin: I did. I took a small group of people with me and I hired over the years, other postdocs. I worked generally on very high-risk projects with a small group of people. I had an NIH grant at Genentech for a couple of years. I supported most of my lab on a grant, and then after that wound down and I supported it on the research budget. There was a fair amount of technology development that was going on with the lab.

I had been working on gene therapy for immunodeficiency diseases when I left the university, and I gave that up as soon as my grant for that expired. I didn't feel that that was a good investment of Genentech's resources. I thought there were too many issues of trying to commercialize gene therapy, if you will. I believed the technology could be developed, but I just didn't think it was commercially viable. At a gene therapy company, that's fine, but not at Genentech.

I kept my lab pretty much up until the time I left. I used to try to spend Fridays working at the bench in the lab. I'd go in and make a mess, and one technician, usually Steve Williams, would go clean it up over the weekend, and next Friday I'd go in there and play again. What was useful was to be looking at primary data from my own lab all the time. It just kept me on my toes, and I could maintain my ability to troubleshoot and interpret my own data, and that helped me when looking at other people's data. When it's your own, one's investment in getting the right interpretation is always much deeper.

Hughes: In the very beginning, Genentech did not have a scientific advisory board. I guess Herb Boyer was the scientific advisory board.

Martin: Hm-mmm.

Hughes: Was there a scientific advisory board in place when you arrived?

Martin: No, that's something I put together.

Hughes: Was it?

Martin: Right.

Hughes: And what was your thinking there?

Martin: It was actually pressure that came from our board. I think it came from Tom Perkins, because he was seeing other biotechnology companies that had scientific advisory boards and we didn't. So as I recall, coming out of one of the board meetings, Bob asked me to put together a scientific advisory board. It was a fairly large board; we had about ten people on it, as I recall. We met a couple times a year, and I learned there how not to run or organize a scientific advisory board.

Hughes: What do you mean?

Martin: The way we did dealt with SAB was to get them together about twice a year for a day or two, and review for them what we were doing. They went away a hell of a lot smarter, and we didn't come out much smarter. We were teaching them. They were very good scientists and good friends. It's just that in a large group like that with a show-and-tell

or a dog-and-pony show it is not very productive. So I ended up breaking it down a bit and getting the SAB members to spend individual time at the company. When I left and went to DuPont Merck, I set up an SAB there and we would get together a couple times a year. However, the major use of members was as individual consultants, where we put them in a room with a few of our scientist for two or three hours and then another small group, maybe a two or three groups a day. Then everyone gets something out of it. At Genentech the big meetings were nice social occasions, nice to see your friends and talk about science, but it really weren't very useful scientifically to the company. I don't think that Bob or the board or anyone else really benefited from that, other than being able to list the members of the scientific advisory board in the annual report and gain some credibility.

Hughes: I think in the early days, I'm thinking of the Biogen board, for example—

Martin: It was a funding mechanism, rather than a working group.

Hughes: Yeah. Exactly. "Look at us, look at all the big names we have."

Martin: At that time when I went to Genentech, we didn't need that funding. We weren't trying to raise money from venture capitalists, so the advisory board was not useful that way. The only way it could really be useful was to provide some useful constructive criticism to management about what R&D was doing, or try to educate scientists within our group about what's going on outside that we had missed or we hadn't thought of. But in a large group, that feedback doesn't work very well.

Hughes: What were your criteria for choosing people, aside from friendship? [laughs] I imagine you had a lot of—

Martin: Certainly, most of them I hadn't known before the SAB. I knew of them. The criteria were, they had to be first-class scientists and we were trying to cover all the science relevant to Genentech's activities, both from a technical point of view as well as, in many cases, a medical or medical investigative point of view. Hence we had a broad group of people, many of whom knew each other, even though they would be working in different fields.

Hughes: To put it very simplistically, choosing people with the expertise that you needed in one way or another. Not just because somebody had a big name; their expertise you wanted.

Martin: Right. It was a little different than many other companies, where they choose an SAB just based on who has the biggest draw or name. We weren't avoiding that, but we wanted people who were actively engaged in investigative science and intense in their science. So many of them were younger people in their thirties, forties, rather than people in their sixties.

Hughes: Then what about the executive board? What was the relationship of you as vice president of research to the executive board?

Martin: I sat on that board. It had different names at different times, but I sat on the board the entire time I was there. It was mostly Bob's—or Kirk's, when he came in—direct-reports who were on it. It fluctuated in size. We had a full management committee; at

one time we had twenty-one or twenty-two vice presidents, which was just incredible. It started out as a management committee that included all the VPs, and then as that grew we created an executive committee. I guess that's what we called it—I've forgotten. The large management committee met once a month. The executive committee was a small group of people and I think we all got along well. Knew each other well; I still see some of them socially.

Hughes: Did you find yourself arguing for the science?

Martin: Sure.

Hughes: I mean, that was your prime function, was it not? But I would think that, too, just because of our previous conversation at the beginning of this, the vice president of marketing might have had a very different idea than you.

Martin: Hm-mmm.

Hughes: So did sometimes the discussion get fiery?

Martin: I don't recall any particular examples of that. If I had a good argument, I could usually convince Gower, who was the marketing person the entire time I was there. I would usually go convince him or he would convince me before the meeting. So there was enough background chatter going on that rarely was anything brought up that he and I had not already discussed from different perspectives. The type of arguments I can remember having was a big argument with Bob about why we should not move our listing from NASDQ to the New York Stock Exchange. That was a polarized argument.

Hughes: What was your argument?

Martin: My argument was—and I learned it from outside—that, as soon as we did because there were no biotech companies on NYSE, we would be recognized only as a pharmaceutical company not a biotech company and our P/E [price/earning] ratio would drop to the common denominator of a pharmaceutical company. Whereas we were riding with a high P/E as a biotech company on NASDAQ. That happened; we listed and pfffft, the stock price went down significantly, just because investors didn't know how to value the company. Whereas several biotech companies were listed on NASDAQ. But that was an ego issue with Bob, I believe.

Hughes: That's what I was going to ask, what was the motive other than ego?

Martin: It was probably ego. There were more rational arguments given than ego. They were related, there being some funds that won't invest in companies unless they're on the Big Board. They won't invest in NASDAQ stocks. Some major fund managers will only go to the Big Board.

On that issue, I was right. On the next one, I was wrong, in retrospect. When we were really tight on cash, we were discussing starting a daycare center, which was going to cost us up front a million bucks and nearly a half a million dollars subsidy a year. A million dollars to improve the leased space. I was against it, because I didn't want to spend the money that way at that time. I'd rather have the money spent on research,

because I felt it was a better investment for the company than a daycare center. It was interesting. I think almost without exception, the rest of management and I had the same position on it, and Bob didn't. So Bob went on and did it. He was absolutely right. Fortunately the finances soon thereafter were okay, and we didn't have a layoff. But he was correct, I think, in his assessment that this would be a major recruiting tool and a major feather in the cap of the company, distinguishing it from the other pharmaceutical companies, for example.

Hughes: Which it did do. Did it not accomplish those things?

Martin: Yes.

Hughes: And so a million was put into it at that time, which was the late eighties. It was about the time you were leaving?

Martin: Late eighties, yes. It was finished before I left. It was probably '88 because the market had dropped and we were having real problems with tPA, and in '89 we thought seriously about layoffs.

Hughes: That's what I thought. It was a rough period for Genentech.

Martin: In '89, I think it was, we were all set up to have a layoff, just because the revenues of tPA were not there. That was the issue.

Hughes: Were negotiations with Roche for what eventually became the acquisition going on while you were there?

Martin: Yes. In fact, I departed Genentech the day that the deal closed, which was September 19, 1990.

Hughes: I have you down leaving in '88. [reviewing curriculum vitae] Okay. So can you tell me a little bit about all that, the lead up and then the machinations around the acquisition?

Martin: I can tell you a bit about what led into it, which again I thought was interesting and had a lot to do with personalities and egos. Money was tight, but it was not an impossible situation by any means. We'd had a planned layoff, and then aborted it—that was probably in '89. The stock price was down; it had fallen considerably, to sixteen or something like that. It had been up as high as sixty. I think that Bob and Kirk both, and I don't know who was the more dominant or influential person but both were fretting from the stock price demise. They were both trying to figure out how to get that back up, so they could gain some respect and personal wealth, I suspect. I know Fred Frank facilitated the deal, and I think they went to talk to Fred initially about being acquired. He came up with a couple of candidates. All of a sudden Roche was on the scene, Jürgen Drews was there, listening to research proposals and we were told that Roche was interested in a project. And then a few of us were told there was potential M and A [merger and acquisition] activity going on, and that we should tell Roche anything they wanted to understand. Most of the due diligence on R&D was done by Jürgen alone, over the period of about ten days, by just talking with groups of scientists. Then there was the financial due diligence, which I knew was going on, but I only knew it from an

executive committee meeting. I was not involved in it. I can remember before it was announced that it was clear to many people in research what was going on.

Hughes: What, in general, was the feeling amongst the scientists about being acquired by Roche?

Martin: They had been convinced by Bob and Kirk that this was the right thing to do because it was going to put five hundred million dollars cash into the bank, and therefore we could afford to do a lot more research. But most of the senior people in Research had spent time over the previous six or seven years, one way or the other visiting pharmaceutical companies, Roche among them. There was not a lot of appreciation for the culture nor wanting to be part of it. So as a result, there was a lot of "Oh my God, let me out of here, this is not what I joined for," that type of predictable attitude. There were not many people who left before it closed, because of the stock option issue. They knew what the price would be on the stock options; that was predetermined, so everyone wanted to cash out. There was a significant exodus over the six months after the closing. People just voted with their feet. A lot of turnover in that period, and so I think that showed their attitude. Some people went and started other companies; some people just went to other jobs in another company.

Hughes: But yet as it turned out, Roche was and continues to be pretty much hands-off.

Martin: Hm-mmm. I think they did a good job of keeping their hands off, and that was the biggest concern. It wasn't predictable that they would. They had previously acquired Syntex, and so the thought was "Oh my God, they're going to move everybody down to Palo Alto, or they're going to force us to work with the former Syntex outfit." That never happened. They kept the former Syntex group separate. I'm not sure who the engineer of that was, whether it was Drews or someone else, I just don't know. They obviously changed the Genentech board.

Hughes: How did you feel about the acquisition?

Martin: I had spent enough time at Genentech—I had been there at that time for almost eight years—that I was ready to go learn something else. I started looking around for jobs just about the time the acquisition was announced.

Hughes: Was the Roche acquisition the precipitating event?

Martin: That was a major precipitating event. It was not my cup of tea. Kirk had also asked me to step aside as head of R&D and I was going to Chiron that was my planned next stop.

Hughes: And yet, that doesn't happen right away, does it? What was the story there?

Martin: I announced I was leaving. I just had a sports fishing boat built, so I took it and went to the Turks and the Caicos to fish for six weeks during the summer of 1990. I came back in August and was committed to go to Chiron on a handshake as head of R&D. I had been back in the U.S. about three or four days, and Bill [Rutter] and Ed [Penhoet] asked me if I would go to Australia with them, to Canberra, because they were interested in buying the Commonwealth Serum Labs there. I told them, "I just got back. The two of you are going; you don't need me to go with you. I'm going to stay here. Let me get some things in order and I'll show up at work"—that was on a Tuesday or

Wednesday—"I'll show up on Monday, when you're back." I got a call Wednesday afternoon from Roy Vagelos asking me whether I would look at a job at a new joint venture that Merck was forming with DuPont. I didn't know anything about it, because I was out of town and missed the news that they were forming the joint venture. I had been at Merck and had interviewed for the head of research there. They had hired Ben Shapiro, instead. But then suddenly when they formed the joint venture, he called and said, "Why don't you take this job?" So I said, "I've already got a job." He said, "Look, I think you ought to go out and look."

In the meantime, Joe Mollica, who was going to be the CEO of DuPont Merck, called me. I immediately called a friend of mine who was at DuPont in their central research labs, Mark Pearson, and said, "Tell me what is going on. I haven't read the article. I've just gotten these couple of phone calls. Is this for real, and what do you think of it?"

So the short of the story was, I went to Wilmington the next day, and looked at the opportunity. It looked very interesting. It was a five-thousand-person start-up, in effect. Came back, went in and saw Ed and Bill on Sunday, when they got back from Australia and told them I needed to get this DuPont Merck opportunity out of my system, rather than showing up the next day for work. They had a board meeting, as I recall, on Thursday of the coming week, and I had already met their board. They said, "Okay, but can you let us know by our board meeting on Thursday?" I agreed. Kathy and I immediately went back to the Wilmington area, spent two days there, Thursday I picked up the phone, called Bill and said, "I've just taken this job at DuPont Merck." I have to say, on Sunday when I went in to talk to them before I revisited Wilmington and told him I needed to get the opportunity out of my system, they were terrific. They said, "Look, go get it out of your system. You have to look after yourself. No one's going to look after you, your career, and your future the way you will. You can't depend upon us to do that the way you can do it for yourself, so go do it." So I did. Then, after a little over three years there, when things went topsy-turvy at DuPont Merck, I called Bill and asked, "Got a job left there?" So that's when I came back to Chiron, in '94. It was an interesting period.

Hughes: What was the attraction to DuPont Merck?

Martin: I think primarily that it was a way to get into the pharmaceutical industry and see what they did from inside, rather than outside. We had attempted to start a medicinal chemistry program at Genentech. It never flourished, primarily because, again, tPA sales never met the projections. So I never had the experience of participating in pharmaceutical R&D.

[Tape 6, Side B]

Martin: I guess in the eight years I had been out of academe, the perception of the pharmaceutical industry had gone from a pretty bad place to be, to a place that was interesting to me, and had some opportunities for real creativity. Because it was a four- or five-thousand-person start-up, it was intriguing—much more so than a typical job in big pharma. When I started looking for jobs, it was ironic but I had been asked to look at a job at Roche, as head of R&D in Nutley. I went there and it was horrible. I won't bore

you with the details of the interview process, but it was just amazing. I went, "Oh my God, not here." A friend of mine was the CEO there, so I had to treat him politely, but [sighs], I got out of there. But this one, because it was new and I knew that Merck would have an influence on it, and I knew several people in the central R&D group at DuPont who were going to move into this joint venture, I decided it would be a really good learning experience. At the time, my wife, who's a painter, was doing quite well showing in San Francisco but was interested in being closer to New York. So we made the joint decision to go give it a try. We're both from the East Coast originally and we'd been here twenty-one years. We sold our house here and moved back east. Scuttled our ships after landing on another shore.

Hughes: And how did it turn out?

Martin: I learned an enormous amount. By that time I had made enough mistakes in management at Genentech that I could actually benefit from them, particularly in a new environment where I didn't have the legacy. I'd learned a lot of chemistry, met a lot of really smart people, had another level of management experience in the industry. At Genentech, we had some really smart people, but most of them were not particularly seasoned. Whereas I was exposed to some very seasoned people who had enormous experiences. While I frequently didn't agree with them, I at least could benefit from their experience. I also had access to Merck in a very unusual way, in that I essentially had a carte blanche to almost any meeting they were having, and used that as a terrific learning experience as well. And yet I didn't have to report to Ed Scholnic, who was a friend of mine and had been for many years. In fact, I maybe mentioned he and I had initiated the negotiation of the sale of the land that all the research buildings at Genentech are now on, at the time when we were trying to negotiate an AIDS vaccine with Merck. So that was a really good experience.

I had easy access to Roy Vagelos. I saw him frequently. I had dinner once a month without fail with Ed, just the two of us somewhere talking about what one does in this situation or that situation. So it was a very unusual three years. At the end of '93, Vagelos became a lame duck, and the budget for '94 for DuPont Merck was being whittled down significantly, particularly R&D budget. They wanted to take forty-five million dollars out of our three-hundred-million-dollar budget, which was a big, big hit. Mollica, the DuPont Merck CEO, didn't want any part of that. We had a partnership board, not really a board of directors consisting of three people from Merck and three people from DuPont. They were going to let that happen, and so the management of DuPont Merck, those of us who were on the executive committees encouraged Joe not to let it happen, to lay down in front of the bulldozer. He did and they ran over him. [laughs]

In the meantime, my wife was unhappy living in that area. It's a tough area to live in; it's very beautiful, but it's very, very conservative. She had decided that we just had to get out of there, and kept pressuring me, "Figure a way to get out of here." Meantime, I started talking to Bill Rutter about if I were to come back, would there be something at Chiron for me? So Joe got run over by the bulldozer, I remember his telling me at a reception the day that it happened, in December of 1993. Earlier my concern about leaving was that I had recruited a number of people and I had a loyalty to them. I didn't want to desert them, but all of a sudden with this change and Joe leaving, et cetera, I decided it was a time to get out gracefully. I announced my resignation about a week

later, and in the meantime had finished negotiations with Bill and Ed to come back into Chiron and run their therapeutics business, running the business rather than just running R&D. So Kathy and I up and left on pretty good terms, I think, with those people. Mollica, who then went to Pharmocopeia, and I remained friends and he tried to acquire Eos [Biotechnology] many years later. That fell through, not because Joe and I didn't want it—we wanted it—but there was a number of issues. I maintained a good relationship with Joe and many other people whom I still see from DuPont Merck. It was a very good experience. I learned a lot about that industry and about management, particularly managing larger entities and groups of people, more complex systems.

Hughes: Interesting, too, from a wider standpoint of academia's general—or used to be—sort of highbrow attitude toward science in the pharmaceutical industry. From what I'm getting from your experience, it wasn't that way at all, that there was top-notch people doing—

Martin: They weren't all, but there were plenty of really smart people there. I think they were a smaller fraction than, for example, we had at Genentech, but there was still a whole lot to learn from very smart people.

Hughes: What about what I'm imagining had to be a difference in corporate structure, just if nothing else because of the size differential? What did that do to the way research was done?

Martin: I did not get nearly so close to the research there as I had been at Genentech, and I didn't have a lab there. I decided I couldn't possibly have a lab and be fair about it. But I still had a limited number of direct reports, like seven or eight, not more than that, which is about the same number that I had at Genentech. It's just that they had much more depth in their own organizations, and we had a lot more projects. There was probably a lot more science to learn. I learned a lot more about clinical trials there because we had a lot more going on and greater regulatory depth. We had more trials going on, in more therapeutic areas. So that was all a very good experience. More interactions with the FDA.

Hughes: You come to Chiron in January of 1994, I remember.

Martin: Right.

Hughes: What did you find?

Martin: I found first of all a very strong anti-pharmaceutical attitude, anything that the pharmaceutical industry did was bad, and they couldn't possibly have any useful ideas about management, science, culture, or anything else. I was surprised by that.

Hughes: This was across all the different departments?

Martin: It was from the top. It was Bill's attitude. I found what in effect was a research institute with very little focus, very little discipline in terms of killing projects or even dealing with performance problems. It was a very soft place, in that sense. There was some excellent science going on, but it wasn't focused, wasn't directed. I had started recruiting a former colleague of mine from DuPont Merck who had told me he was interested in leaving also. He had been a VP of strategic planning and operations for

R&D in DuPont Merck. I wanted to recruit him to Chiron to do a similar thing for the therapeutics group. He was all ready to come, and I'd been there about two or three months and saw what was going on. I called him and said, "You know, it's not what meets the eye. I'm not sure you really want to come; you need to have your eyes wide open." He had been in the pharmaceutical industry much of his career, and I said, "There's such an anti-pharma attitude here that you'll probably be persona non grata. I'm getting by because I didn't start in pharma, but I have to be really careful making suggestions. I could never say, 'Well, in my experience at DuPont Merck—' because, you know, deaf ears." At least it appeared to be deaf ears everywhere, and I knew Bill's were. He just didn't want to touch it. This person, who ended up joining Chiron anyway, said, "Look, I've got to get out of here. It's a ticket to California, so I'm going to come to California." I ended up leaving Chiron after fifteen months.

Hughes: April of 1995.

Martin: Right, the end of April. So I was there fifteen months. While I'd known Bill for over twenty years at that point, I'd never actually worked for him. I'd worked for the Department of Medicine, for Holly Smith, and had a joint appointment in Biochemistry at UCSF. Bill and I had gotten along very, very well. But I discovered, having to work for him, he had these very strong biases and a style of management that was very difficult to contend with.

Hughes: Meaning that he made the decisions?

Martin: Yes. For example, he would have a management committee meeting, and called it a "strategy committee" or something like that, and there would be an agreement in the room, consensus in the room except for Bill, and everyone in the room would think, "Okay, this is where we're going to go." However, within an hour or two after the meeting had been adjourned and the decision, we thought, had been made, Bill would go talk to every individual and undermine the decision. That was his style; he's a real crisis manager. He's a very good crisis manager, but he seemed to turn everything into a crisis in order to get his opinion implemented. I just decided that the friendship and the relationship we had was going to be destroyed if I stayed there, because I was going to constantly argue with him. I left and went to Lynx [Therapeutics, Inc.] at that point, where he warned me not to go. I should have listened to him, because he knew Sam Eleter and had had some really difficult dealings with Sam, who was Lynx's chairman and CEO at the time I went there. I went there anyway and lasted eighteen months.

Hughes: [laughs] And what were you doing there?

Martin: I was CEO. Sam was chairman of the board. The board had told me, "Don't worry, we'll take care of Sam for you. We know he's a difficult person, but you're our person and we'll protect you on this." Sam was a street fighter, and I think the coup de grace, the final thing for him, as a paranoid man, he became convinced that Sydney Brenner and I were conspiring to conduct a secret project. Therefore I was being disloyal and dishonest with him. He didn't fire me; he had the board come tell me they needed my resignation suddenly one day. Of course, Sam knew everything Sydney and I were doing and he had actually been invited to the meeting that was being held the next week where we were bringing out a scientist to talk about biology project, and he had also heard the preliminary interest, et cetera. He just had to think of an excuse to get rid of

me because, again, I would not let him get by with what he wanted to get by with. The company has gone completely down the tubes since, unfortunately. They finally threw him out. He is a smart engineer, but difficult person. Bill knew that and Bill kept warning me, "Don't go there. Stay here, don't go there." I made that mistake.

Then Heyneker and I started Eos right after that. In fact, immediately after being fired by the Lynx board, I was on the BART train and called Herb on my cell phone. I said "Okay Herb, let's do it by ourselves." I had him involved in this effort to import biology to Lynx. He had introduced me to Steve Weiss, who became a co-founder of Eos with Herb and me. It was bringing Weiss in and trying to import some biology into Lynx that Sydney and I wanted to do. That way we could begin to use some of the Lynx instrumentation that Sydney had invented. We wanted to actually ask some biological questions. We felt that Steve had some very nice model systems that we could use.

Hughes: So that became Eos.

Martin: Right. We took the concept out of there, which Lynx never built because Sam couldn't understand it. We started using AHy metrix DNA chips rather than the sequencing equipment that Sydney had come up with, MPSS [massively parallel signature sequencing].

Hughes: Two more minutes to bring this right up to date with ProtoGene.

Martin: GangaGen.

Hughes: Where did I get ProtoGene?

Martin: ProtoGene was a Heynecker Company that preceded Eos and Array Technologies.

Hughes: I'm sorry. At least I got the "gene" part right.

Martin: So a friend of mine from UCSF, J. [Janakiraman] Ramachandran, had gone to Genentech in the protein biochemistry department after I went there, had spent a lot of time in India and established the Astra research institute there. He retired from there after it became AstraZeneca back in 2000, and started a phage therapy company, which he named GangaGen. He came to talk to me about what he was doing, asked me whether I'd join his board. I was on too many boards, but I left one board and joined his board. Then when the Eos/PDL [Protein Design Labs] merger was closing, I realized I was going to have extra time, so I agreed to take the chair of that board. I did so about a year ago, I guess. A year and a half ago, maybe.

Hughes: [consulting CV] This says 2003.

Martin: Yes, 2003. It was about a year ago. So then the board asked me if I would take the CEO position and I hesitated for some reasons and finally agreed in the fall of 2003 to do that. This is a company that's focused on using bacteriophage to treat bacterial infections in humans and in the food chain by treating feedlot cattle, for example, to get rid of *E. coli* 0157:H7.

Hughes: That work goes way back in history.

Martin: Oh yes, more than a hundred years. There's some wonderful medical history.

Hughes: [Felix] d'Herelle.

Martin: D'Herelle, right. [Ernest Hanbury] Hankin, even before d'Herelle.

Hughes: Isn't that amazing how history comes full circle?

Martin: There's some wonderful medical history there, some very clever clinical trials that d'Herelle did. Very, very clever.

Hughes: Is that so? He really pushed that for his lifetime.

Martin: Yes, absolutely. It was great biology.

Hughes: I wish there were time to hear part of it.

Martin: GangaGen has a good website, has all that history and translations from French.

Hughes: Either that, or give us both five years and we'll continue the saga.

Martin: That's right.

Hughes: Well, I thank you, Dave. I should ask you my usual wind-up question, though. At this point—and I realize you've got more to come—what contribution are you proudest of?

Martin: Well, certainly the number of people I trained in academe as postdocs. That was a really very productive time. Genentech was also a highly productive time and I just learned a lot. In fact, I think that every product that Genentech has in the market, including the recent ones, have either been in-licensed or were started on my watch, Avastin being one of them. I very enthusiastically supported the hiring Napoleone Ferrara out of UCSF to get that project going. Thrombopoietin, we'd started. HER2, et cetera. The only one that I had absolutely nothing to do with was the in-licensed one from IDEC, the anti-CD20 monoclonal antibody.

Hughes: Rituxan?

Martin: Rituxan, right. That was in-licensed after I left.

Hughes: That's a pretty good record.

Martin: Not a bad record. A lot of products coming out of research; a good yield.

Hughes: I thank you.

Martin: You're very welcome.

[End of interview]

Transcriber: Sarah Wheelock
Final Typist: Jackie Thornton

David W. Martin, Jr., M.D.

Curriculum Vitae

Home: 281 Chestnut St..
San Francisco, CA 94133

Work: 225A Gateway BlvdSouth San Francisco, CA 94080
650/246-2302
dmartin@eosbiotech.com

Personal Information

Date of Birth: January 15, 1941
Place of Birth: West Palm Beach, FL
Marital Status: Married, two children

Education

1958–1960 Attended Massachusetts Institute of Technology
Cambridge, MA

1960–1964 M.D., Duke University
Durham, NC

Research and Professional Experience

1962–1963 Post-sophomore Fellow
Research Training Program
Laboratory of James B. Wyngaarden
Duke University Medical Center
Durham, NC

1964–1965 Internship in Internal Medicine
Duke University Medical Center

1965–1966 Assistant Resident
Department of Medicine
Duke University Medical Center

1966–1969 Research Associate
Laboratory of Gordon M. Tomkins
Laboratory of Molecular Biology
National Institute of Arthiritis and Metabolic Disease
Bethesda, MD

1969–1970	Instructor Department of Medicine and Department of Biochemistry and Biophysics University of California, San Francisco
1970–1975	Assistant Professor of Medicine and Chief, Medical Genetics Service Department of Medicine University of California, San Francisco
	Lecturer Department of Biochemistry and Biophysics University of California, San Francisco
1974–1982	Investigator Howard Hughes Medical Institute Executive Offices: Miami, FL
1975–1979	Associate Professor of Medicine in Residence and Chief, Medical Genetics Service Department of Medicine University of California, San Francisco
	Associate Professor of Biochemistry in Residence Department of Biochemistry and Biophysics University of California, San Francisco
1977–1978	On sabbatical leave Laboratory of Henry Harris and Richard Gardner Sir William Dunn School of Pathology Oxford University Oxford, England
1978–1982	Director Medical Scientist Training Program (M.D./Ph.D.) University of California, San Francisco
1979–1982	Professor of Medicine in Residence Chief, Medical Genetics Service Department of Medicine University of California, San Francisco
	Professor of Biochemistry in Residence Department of Biochemistry and Biophysics University of California, San Francisco
1983–1988	Vice President, Research Genentech, Inc. South San Francisco, CA
1983–Present	Adjunct Professor of Medicine and Biochemistry University of California, San Francisco

1988–1989 Senior Vice President, Research and Development
Genentech, Inc.
South San Francisco, CA

October 1990– Director, Research and Development
December 1990Pharmaceuticals

E.I. du Pont de Nemours & Co., Inc.
Wilmington, DE

January 1991- Executive Vice-President

December 1993 Research and Development

DuPont Merck Pharmaceutical Company

Wilmington, Delaware

January 1994– Senior Vice President
April 1995 Chiron Corporation

President, Chiron Therapeutics
Emeryville, CA

May 1995– President & Director
December 1995 Lynx Therapeutics, Inc.

Hayward, CA

January 1996– President, Chief Executive Officer
November 1996& Director

Lynx Therapeutics, Inc.
Hayward, CA

1997–2003 President & Chief Executive Officer
Eos Biotechnology, Inc.
South San Francisco, CA

2003-present Chairman & Chief Executive Officer
GangaGen, Inc.
San Francisco, CA

Boards

Member Recombinant DNA Advisory Committee
National Institutes of Health, 1981–1985

Member Research Development Council
Cystic Fibrosis Foundation, 1983–1987

Member Committee on Public-Private Sector Relations in Vaccine Development
Institute of Medicine of the National Academy of Sciences, 1983–1985

Member Board of Overseers
Duke University Comprehensive Cancer Center, 1985–1988

Member Advisory Committee for the University of California Biotechnology Research and Education Program, 1986–1990

Member Forum on Drug Development and Regulation
Institute of Medicine, National Academy of Sciences, 1987–1995

Member UCLA Symposia Board, 1986–1990

Member Roundtable for the Development of Drugs and Vaccine Against AIDS
Institute of Medicine, National Academy of Sciences, 1989–1991

Member Scientific Advisory Board
Center of Molecular Medicine
University of Oklahoma Health Sciences Center, 1989–1991

Member Scientific Advisory Board
Ernest Gallo Clinic and Research Center
University of California, San Francisco, 1989–1996

Member Board of Scientific Counselors
Division of Cancer Treatment, National Cancer Institute, 1990–1993

Member Advisory Board of the Center for Health Sciences
University of California, Irvine, 1991–1993

Member Board of Trustees
University of Pennsylvania Medical Center, 1991–1994

Member Board of Directors
National Association for Biomedical Research
Washington, D.C., 1991–1996, Chairman, 1995–1996

Member University of Pennsylvania Medical Center Board of Overseers of the School of Medicine, 1991–1994

Member Health Sciences Policy Committee
Institute of Medicine, National Academy of Sciences, 1992–1996

Member Board of Directors
Varian Associates, Inc., Palo Alto, CA, 1993–1999

Member Board of Directors
Ribozyme Pharmaceuticals, Inc., Boulder, CO, 1994–1995

Member Board of Directors
Cell Therapeutics, Inc., Seattle, WA, 1995–1997

Member Board of Directors
Genovo, Inc., Philadelphia, PA, 1995–1996

Member Board of Directors
Telik, Inc., South San Francisco, CA, 1997–2001

Member Board of Directors
Cubist Pharmaceuticals, Inc., Cambridge, MA, 1997–present

Member Board of Directors
Millennium BioTherapeutics, Inc., Cambridge, MA, 1997–1999

Member Board of Directors
Varian Medical Systems, Inc., Palo Alto, CA, 1999–present

Member Board of Directors, Chair

GangaGen, Inc.

San Francisco, CA and Bangalore, India, 2001-present

Member Board of Directors

Bay Area Bioscience Center (“BayBio”), South San Francisco, CA, 2002-present

Editorial Boards

Editor Harper's Review of Biochemistry
Editions 18, 19 and 20
Lange Medical Publications
Los Altos, CA, 1980–1985

Science Year
World Book Encyclopedia, 1981–1986

Journal of Biological Chemistry, 1983–1988

Societies

Alpha Omega Alpha Honorary Medical Society, elected 1963

American Federation for Clinical Research, elected 1974

Western Society for Clinical Research, elected 1973

American Society of Biological Chemists, elected 1974

American Society of Clinical Investigation, elected 1976

Western Association of Physicians, elected 1979

Association of American Physicians, elected 1982

Honors

Distinguished Alumnus
of the Duke University School of Medicine, 1985

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Chapter 29: Metabolism of Purine and Pyrimidine Nucleotides
Chapter 30: Metabolism of Nucleic Acids
Chapter 31: Protein Synthesis and the Genetic Code
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