Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Program in Bioscience and Biotechnology Studies

STEVEN ROSENBERG, Ph.D.
EARLY SCIENTIST AT CHIRON CORPORATION

Interviews Conducted by
Sally Hughes, Ph.D.
in 1992

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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Steven Rosenberg at Chiron Tenth Anniversary Picnic, Knowland Park, Oakland, California July 20th, 1971 (the day before the Cetus merger).

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BIOTECHNOLOGY SERIES HISTORY

Genesis of the Program in Bioscience and Biotechnology Studies

In 1996 The Bancroft Library launched 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, Bancroft had no coordinated program to document the industry or its origins in academic biology.

When Charles Faulhaber arrived in 1995 as Bancroft's 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 and the pioneers 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 and archival 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 plans to safeguard the archives of individuals and businesses making significant contributions to molecular biology and biotechnology. 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 has been 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 publicity through ROHO news releases and announcements in scientific, medical, and historical journals and newsletters and via the ROHO and UCSF Library Web pages.

Oral history as a historical technique has been faulted for its reliance on the vagaries of memory, its distance from the events discussed, and its subjectivity. All three criticisms are valid; hence the necessity for using oral history documents in conjunction with other sources in order to reach a reasonable historical interpretation.[1] Yet these acknowledged weaknesses of oral history, particularly its subjectivity, are also its strength. Often individual perspectives provide information unobtainable through more traditional sources. Oral history in skillful hands provides the context in which events occur--the social, political, economic, and institutional forces which shape the course of events. It also places a personal face on history which not only enlivens past events but also helps to explain how individuals affect historical developments.

Emerging Themes

Although the oral history program is still in its initial phase, several themes are emerging. One is "technology transfer," the complicated process by which scientific discovery moves from the university laboratory to industry where it contributes to the manufacture of commercial products. The oral histories show that this trajectory is seldom a linear process, but rather is influenced by institutional and personal relationships, financial and political climate, and so on.

Another theme is the importance of personality in the conduct of science and business. These oral histories testify to the fact that who you are, what you have and have not achieved, whom you know, and how you relate have repercussions for the success or failure of an enterprise, whether scientific or commercial. Oral history is probably better than any other methodology for documenting these personal dimensions of history. Its vivid descriptions of personalities and events not only make history vital and engaging, but also contribute to an understanding of why circumstances occurred in the manner they did.

Molecular biology and biotechnology are fields with high scientific and commercial stakes. As one might expect, the oral histories reveal the complex interweaving of scientific, business, social, and personal factors shaping these fields. The expectation is that the oral histories will serve as fertile ground for research by present and future scholars interested in any number of different aspects of this rich and fascinating history.

Location of the Oral Histories

Copies of the oral histories are available at the Bancroft, UCSF, and UCLA libraries. They also may be purchased at cost through the Regional Oral History Office. Some of the oral histories, with more to come, are available on The Bancroft Library=s Program in Bioscience and Biotechnology Studies Website: http://bancroft.berkeley.edu/Biotech/.

Sally Smith Hughes, Ph.D.
Historian of Science

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
October 2002

1.The three criticisms leveled at oral history also apply in many cases to other types of documentary sources.

October 2005

ORAL HISTORIES ON BIOTECHNOLOGY

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

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

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

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

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

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

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

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

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

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

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

David Martin, M.D., *UCSF Professor, Genentech Vice President of Research and Beyond, 2005*

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

Diane Pennica, Ph.D., *t-PA and Other Research Contributions at Genentech*, 2004

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

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

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

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

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

Steven Rosenberg, Ph.D.: *Early Scientist at Chiron Corporation,* 2005

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

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

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

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
David Martin
Arthur Riggs
William J. Rutter, volume II
Axel Ullrich
Mickey Urdea
Pablo Valenzuela
Keith R. Yamamoto
William Young

INTERVIEW HISTORY—Steven Rosenberg

Steven Rosenberg was interviewed more than a decade ago to document his role as one of the earliest scientists at Chiron Corporation. When the Chiron oral history project was launched in 2004, the oral history was finalized and included in the series. Three short interviews were conducted in 1992 in Dr. Rosenberg's office during lunch breaks, interrupted by forays into the adjoining laboratory to check experiments. Relaxed and forthcoming, he talked with particular vivacity about the company's formation and founding project on hepatitis B vaccine. Because Rosenberg's career at Chiron spans two decades, his oral history documents Chiron's growth from a small research operation based largely on expertise in yeast biochemistry and genetics to a multinational corporation with several thousand employees and three distinct businesses. Rosenberg became Senior Scientist in 1986, and Director of Biological Chemistry at Chiron in 1992, and in 2001 left the company to pursue opportunities in drug design. He is presently Chief Scientific Officer at Expression Diagnostics (XDx), Inc.

The Regional Oral History Office was established in 1954 to augment through tape-recorded memoirs the Library's materials on the history of California and the West. Copies of all interviews are available for research use in The Bancroft Library and in the UCLA Department of Special Collections. The office is under the direction of Richard Cándida Smith, Director, and the administrative direction of Charles B. Faulhaber, James D. Hart Director of The Bancroft Library, University of California, Berkeley.

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Historian of Science
Director, Program in Bioscience and Biotechnology Studies

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

INTERVIEW WITH STEVEN ROSENBERG

I EVENTS BEFORE CHIRON

Education and Early Career

[Interview 1: September 11, 1992] [Tape 1, Side A]

Rosenberg: I started out my career in science when I was an undergraduate at Brandeis University, where I majored in chemistry and finished my degree in 1973. I came out to Berkeley at that point for graduate school and did my Ph.D. in the Department of Biochemistry at Berkeley with Jack Kirsch, who's an enzyomologist--really doing physical chemistry on enzyme mechanisms. I then spent an additional three years at Berkeley working with Mike Chamberlin on the mechanism of transcription, specifically how *E. coli* RNA polymerase recognizes sites on DNA that are important for gene regulation.

Around the end of 1980, I started thinking about looking for jobs. Real jobs. Postdocs get paid a lot better than graduate students. They make twelve thousand dollars a year on a fellowship, which wasn't taxable, and so I felt quite wealthy. But that was still not a lot of money, even in those days. I had looked at a number of jobs in academia around the country--not in the Bay Area but in southern California and also on the East Coast. But my fiancée, now wife, said, "Why should I go live in pick-your-unappetizing-place-to-live-choice when you're going to spend all of your time in the lab anyway?" Which was a fateful statement and probably an accurate one, too.

Amgen North

At that point, I started thinking about possible alternatives, and I had been talking with Patty Tekamp, now Patty Olson, who was a good friend of mine at the time. We had been in graduate school together. She was a graduate student with Ed Penhoet and was at that time a postdoc with Bill Rutter. She said, well, George Rathmann was trying to organize a company and that it was possible that a number of people in Rutter's lab at UCSF might be involved in this.

Hughes: Who is Rathmann?

Rosenberg: George Rathmann was the first chairman of Amgen. I knew one of the other participants in the early stages of Amgen, Marv[in] Caruthers, who invented the chemistry that people now use to make oligonucleotides to make synthetic DNA. He was both a founder of Amgen and also of Applied Biosystems and actually holds the original patents in that regard. I knew Marv pretty well from his having hung around the lab where I was a postdoc trying to learn how RNA polymerase bound DNA, and Marv wanted to know what DNAs they ought to make now that they could make DNA.

We got to be pretty good friends, so I said, "Well, I'll send a letter to Marv Caruthers and ask him what's going on with this [company]." And so this letter, which I'll give you a copy of, came out of that. Essentially, it's a letter [from me] to Pablo Valenzuela, who is now the executive V.P. of research at Chiron and has been the research director since its inception. It's dated the beginning of May of '81--sending him my resume saying I'm interested in what we then called Amgen North, which was going to be a branch of Amgen in San Francisco.

[I] talked to Pablo then about a meeting in Monterey which was about ten days hence where Pablo and I were going to go, and a number of other people from Chiron--well, it wasn't Chiron yet--what was to be Chiron--would be there. We arranged that we would meet there. I had already sent a copy of my resume to Marv Caruthers, and he was going to forward it to George Rathmann, who had had a number of discussions with a group of people at UCSF about becoming part of Amgen.

Hughes: Do you know who?

Rosenberg: Yes. Pablo, Graeme Bell, Rob Hallewell, George Kuo, Leslie Rall--and Patty Olson was involved in it somewhat. I'm trying to think if there was anyone else. That was, I think, the core group of people.

What happened in the interim, from this letter which was dated May 8th, was that the people at Amgen, at least as I have been told the story, decided that it was going to be too complicated to have two research groups, one in southern California in Thousand Oaks where Amgen was located, and one in San Francisco.

At some point later in that month, Bill and Ed Penhoet decided, with Pablo, that they didn't really need other people to finance this, that given the work that had previously gone on in Bill's [UCSF] lab on cloning the insulin gene and then very recent work, which was somewhat supported by Merck, on the hepatitis B surface antigen expression in yeast, that maybe they could do this themselves. So quoting from this letter, "...hope to be able to discuss the prospects at Amgen with you then." Well, Amgen became Chiron. Amgen obviously became very successful in its own right. It's amusing to think that if they had combined to be one company, if it had been successful, it clearly would have been the most successful biotechnology company. But that wasn't meant to be.

II FOUNDATION AND EARLY YEARS OF CHIRON

Rosenberg Joins Chiron

Rosenberg: In fact, at that meeting on promoters in Monterey ten days later, Pablo and Graeme and Rob Hallewell and I had lunch at Fisherman's Wharf down there, and Pablo offered me a job if I was interested. He said, "Yeah, if you want to join us, sure." So that was the way we offered jobs. No seminar. No anything. That was that. This went back and forth in a state of some uncertainty for a few months. I was also getting married two months after that, at the end of July, and finishing my postdoc and wasn't quite sure what was going to happen. But it all ended up working out. Somewhere I probably still have my offer letter where they offered me what I thought was a very generous salary. It was about triple what I was making as a postdoc--and some options.

Hughes: Was that par for the course for the industry?

Rosenberg: I think it was probably. One of my friends in academia reminded me that at that point--this was 1981--they were offering me, starting, what a senior associate professor was making at Berkeley. So I thought it was fantastic. I never thought I'd make that much money. They also offered us a chance to spend a few dollars and buy some stock in this company which didn't exist yet, which none of us thought very much about because we were all very naive. If we had thought about it, we all would have asked for more. But we didn't. We ended up having to write a check for fifty dollars to get these shares, which didn't exist yet, and to wait around for the company to start.

I thought about going to Genentech, or to Cetus actually. A couple of people were telling me that I was crazy to go to a new start-up. I was throwing away my career. If I'm going to go to a company, I really ought to go to one that has been around for a while.

Hughes: Why didn't you?

Rosenberg: My attitude was: I had just finished my postdoc; I was only twenty-nine; I figured, I'll spend a couple of years; I'll learn a lot of interesting stuff. It was clearly a bright group of people. If the company goes belly-up, I'll just go do another postdoc. I had only

done one postdoc at that point, and I would learn a lot of stuff that I wanted to learn anyway, so it was a good opportunity.

Chiron in Berkeley

Rosenberg: Well, through the months of June and into July, Chiron didn't have any labs. It had a small office, which was on Domingo Street in Berkeley, up above the Bread Garden Bakery.

C.K. Chang, who had been one of the business managers at UCSF, was Chiron's first business manager. He's quite a character. I'm sure you'll get lots of stories about C.K. One of them is I think worth noting. He came from a very wealthy Taiwanese family. His father was in fact the Taiwanese ambassador to the U.S. at one point. They owned probably at this point a few billion dollars worth of real estate in L.A., but C.K. wasn't interested in managing that. He got off doing other things. He was a director of several of the companies that his family controlled, so he would always be running off to a board of directors meeting, when he wasn't ordering things like pipette tips and this and that. He had a telephone, a chair, and an ashtray, and that was Chiron's address.

Several people later on showed up at this office for interviews. They were coming because at that point we had some labs. It was pretty amusing: This was the mailing address, but there wasn't anything there. I think it happened that one person in fact got there and said, "This must be some hole-in-the-wall," and left and never showed up.

Laboratory Space in Emeryville

Rosenberg: I got married at the end of July. My wife and I took two weeks off for our honeymoon. Chiron had at that point rented some laboratory space in Emeryville. We were subletting this space from a company called Biopolymers. Bill was on the board with Charlie Crocker of the Crocker Bank family and a few other people. Biopolymers was run, scientifically, by Mickey Urdea who is a director at Chiron now in DNA probes, and a few other people, all of whom are still at Chiron. We were renting space from them while they were renting space from Cetus. This was all in the old Cetus building, the Oldham Building. So there we were. We had two small labs and about seven or eight people all of whom started about the same time.

Hughes: All scientists?

Rosenberg: They were all scientists.

Hughes: Except for C.K.

Rosenberg: C.K. was the only nonscientist, and he wasn't there very much. There were a number of people who had been at UCSF who moved over, because we were very concerned about

conflicts of interest and this and that. It was a dicey period in the sense that here are all of these people moving from UCSF. They were really working for Chiron at this point, and we were trying to get them out of UC, and it took a while to get everyone moved over here. As a matter of fact, a lot of people didn't move over until January [1982] when we moved to what were then our new labs.

Hughes: Were there issues of intellectual property?

Rosenberg: I don't think there were issues of intellectual property, but it was just uncomfortable. You had people still in Bill's lab, who were working at the university, so you didn't want to have things commingled, or you wanted to have them commingled as little and for as short a time as possible.

Hughes: Had the tensions that were apparent in the Department of Biochemistry calmed down?

Rosenberg: I wasn't that in touch. That was focused largely between UC and Genentech.

We had these two small labs stuffed full of stuff, trying to get work done. It was pretty amusing because people who were then at Cetus had heard that there was this new company which was renting space in the building, and you better be careful not to talk in the halls, and all of this stuff. They wouldn't let us eat in the cafeteria, and there was no place to eat in Emeryville. We drove to North Berkeley to eat lunch.

We had these two little holes in the wall, and we had this one little conference room off it. There were these open, uncapped steam pipes. Sometimes, I guess, the heat would turn on and off in the building, and you could see these puffs of steam coming out of this thing. We would have people coming to give job interview seminars in this conference room with these puffs of steam coming out, and it was quite a scene. You had people from some of the best universities in the country coming to give job seminars, and they'd be looking around as they were giving their talk at these puffs of steam and thinking, who are these guys, anyway?

One of the most amusing things was, Lacy Overby from Abbott was one of Chiron's early vice-presidents of diagnostics--the person at Abbott who developed the blood-screening test for hepatitis B which really made Abbott the diagnostics power that it still is today, though Chiron is now a close second. Lacy was sort of a consultant of ours in that field, and actually came later as an employee. When he was in the area, he would come by and visit us. It was just really incongruous to have this guy who was a V.P. at Abbott seeing all of these long-haired maniacs trying to do crazy science and make a vaccine.

Hughes: Well, he must have appreciated you or he wouldn't have kept coming back.

Rosenberg: Well, I think that's true, but the setting was pretty incongruous. I remember especially that Tony Brake, who had been at Berkeley at the same time I was, came down for an interview. I still remember him looking around at the pipes and the steam coming up and just sort of shaking his head.

The Hepatitis B Vaccine Project

Adopting a Yeast Expression System

Hughes: What research were you doing?

Rosenberg: What I knew a lot about at that point was how genes in *E. coli* are expressed. So I was trying to develop some new vectors for getting really good expression in *E. coli*. That was a side technology project. Mostly, we were working on hepatitis B.

Hughes: Is hepatitis B the project that made Chiron possible?

Rosenberg: Yes. That technology was licensed. It was originally supported by Merck. I don't know how all the patents and this and that worked out. But the original discovery had been a joint discovery between Bill's lab and the lab at the University of Washington.

The guy there [Ben Hall] had the earliest patents on expressing hepatitis B surface antigen in yeast. It turns out, unlike a lot of proteins, it doesn't work in *E. coli* because it needs to form a particle, like a virus shell, in order to be immunogenic. The monomer by itself is about a thousand-fold less immunogenic. And it turned out that yeast would spontaneously form these particles, whereas *E. coli* wouldn't. So that was a big advantage. In fact, Chiron's subsequent focus on yeast as a means of making proteins by recombinant DNA came down very simply to the fact that the first protein we had to work on, which was hepatitis B surface antigen, only worked in yeast or mammalian cells. And so we worked in yeast.

Support from Merck & Co.

Rosenberg: In that period, Chiron was supported by Merck to improve the process for making more of these hepatitis B particles in yeast. Merck was very concerned because they had spent a lot of time and money developing a hepatitis B vaccine. It was called Heptavax, which was a very good vaccine, but it was made from [the serum of] people who are carriers of the virus. And, at that point, the story with AIDS was just beginning to emerge. Merck had spent a couple hundred million dollars, and they were going to watch it all go down the tubes because even though there has never been any evidence to this day that anyone who got that vaccine ever was exposed to HIV, no one would take it. Even physicians wouldn't take it. So they really needed a replacement, and this was where the recombinant vaccine was to come from.

The First Scientists

Rosenberg: Well, that fall we didn't get very far in terms of getting experiments done. We still hadn't figured out where we were going to get enough space to move all of the people who wanted to start working with the company over here. There were a number of other people who had decided that they wanted to come join Chiron who were still over at UCSF or at [UC] Berkeley or elsewhere.

Hughes: Well, tell me who was there in that very first group.

Rosenberg: In that first group, Rae Lynn Burke and Patty Tekamp and myself.

Hughes: Are these all biochemists?

Rosenberg: Virologists, biochemists. Rob Hallewell, who had been in Howard Goodman's lab at UC. Leslie Rall. Margarita Quiroga. A research associate of Rob's whose name was Susan something. I think that's about it. Six or seven people. Interestingly, it was about half women, half men. Actually, it may have been more women than men at that point.

The Early Physical Layout of the Company

The main Chiron complex was originally the Shell Oil Research and Development complex. There was an old abandoned building across the street which had been part of this. I remember going over there with Ed Penhoet and Pablo. I don't remember exactly when but this could have been May [1981]. I'm looking in this building, saying to myself, I'm really going to come work here? There were rats. The building had been abandoned for ten years. There were people sleeping in the building.

The best thing about it was that in the intervening ten years a large colony of barn owls had taken up residence in the ventilation system. For probably the subsequent four or five years, until they renovated the buildings, at dusk these barn owls would come out and go hunting. They had five-foot wingspans and they were white. They were just fantastic. We should have made our corporate symbol the owl. Here you were in this totally beaten-down industrial area--much different than Emeryville is now--and these owls would come out. They were probably hunting rats, but anyway, it was just very incongruous. We had originally thought about getting some space in San Francisco, but it was just too expensive, and we figured these labs would be okay. The building was originally built as labs. The building was a real mess.

Hughes: Who was looking for space?

Rosenberg: Ed and Pablo primarily, and probably C.K. had something to do with it. Bill was wheeling and dealing, as usual.

There was a guy named Rich Flowers who was a construction guy. I don't know where we found him, but he was the one who renovated the labs for us, and he did it very inexpensively. He got a bunch of Chiron stock out of it. We probably paid him in stock. He was around for probably the first five or seven years of Chiron, building this and that, another one of the C.K.-like characters who were part of the community but weren't scientists. Finally they had the labs finished. I think the first people moved over into the first lab in December.

Hughes: Of '81.

Rosenberg: December of '81--right.

A number of people from UC needed for visa reasons or whatever to get out of UC and have a real job. Their student visas were up or whatever. The first lab over there was legendarily called Lab 1. Doris Coit and Angelica Medina were both there, and they were people who had worked with Pablo at UC. Then in the beginning of January, all the people who had been in the old Cetus building moved over.

January of '82 saw some of the worst floods in the Bay Area in the previous twenty years. In fact, a couple of people got killed in Marin County because it was also a high tide. I had a little house in Oakland at the bottom of a big hill, and I'd gone and looked in the basement that morning, and there was about four or five inches of water. It was about three inches below the water heater. I thought, Great. The water heater's going to flood out. It's just going to be a disaster. We'd only bought the house about a year before. I said, "Well, I've got to go to work because we've got to move today."

Well, between the old Cetus building, the M Building--now called the Chiron Building--is an overhead walkway. The Cetus people were nice enough to let us push all of our equipment through the walkway to get over to the other building. So that's what we spent the day doing, and it was pouring, the thing [walkway] was leaking, and we were pushing centrifuges and all this stuff over to our new labs. That walkway was walled off for the next ten years, until the Chiron/Cetus merger.

Hughes: Really?

Rosenberg: Yes, because it was a violation of some sort of proprietary interest [to open it up]. There was no communication with us, but that is another thing. Fortunately by the time we got home that evening the rains had subsided enough so the water had run out, and the water heater never flooded. So that was the beginning of January of '82. At that point Chiron might have been twenty-five people--something like that. The majority were from UCSF. There were a few people from Berkeley, not that many, and one or two other people from various and sundry weird places.

Continuing the Hepatitis B Story

The Race for a Vaccine

Hughes: How much scientific direction were you being given?

Rosenberg: I don't remember. [laughter] Everybody was working on trying to figure out whatever ways we could to improve expression of the hepatitis B surface antigen. Merck was the only support we had at that point, and we knew we were in a very tight race with Genentech and probably a few other people about making this vaccine.

Hughes: Did you feel the pressure?

Rosenberg: Oh, yes. Well, Genentech, even at that point had an aura of being the golden boys of biotechnology.

Dino Dina Joins Chiron

I believe it was that spring of '82 Pablo and I went on a trip to Merck--Bill Rutter and Dino Dina. Dino had been a postdoc with Ed and then had gone on to be an assistant professor at Albert Einstein. When he had been at Berkeley, he and I and his ex-wife got to be very good friends and enjoyed lots of drunken dinners together–drank too much wine and generally had a great time. Dino was really unhappy being in New York, though his wife loved it, and really wanted to come back to the West Coast. He's a very good virologist, and I kept telling him, "Listen, you ought to really think about coming to Chiron." Finally one day--it was probably sometime in 1982--we finally figured out a way of getting him to meet Bill at an airport in New York. Bill was on his way somewhere, and so he and Dino met at the airport and ended up convincing Dino some way or another to come out here and join Chiron. Dino is now the head of the Biocine Company, our joint venture with Ciba-Geigy for all the other vaccines for development.

Hughes: What was the attraction to a scientist in those days? Why go to Chiron?

Rosenberg: It was new, interesting science. Dino knew a lot of the people involved. A lot of it was personal interactions. A lot of the reason why Chiron is so concentrated in UCSF and Berkeley is because it got started by people who knew each other.

Hughes: And that's not so true of other companies?

Rosenberg: I think it probably is. I think there's always a core of people who know each other well enough to both respect the other people and trust them. That's really a key, especially early on. People are working so hard that you can so easily get torn to bits by squabbling. We really managed to avoid that to a large extent.

A Trip to Merck

Rosenberg: Anyway, so Bill and Dino and myself--Pablo might have been there--went to Merck. I had become very heavily involved at that point in trying to improve the expression levels, and we had some success. Somehow I got nominated to give the presentation at Merck. We got in about one in the morning, and we were supposed to be at Merck at eight or nine the next morning. We were sitting in some pizza joint--it may have been in the restaurant in the hotel. We'd just gotten in and we were having a discussion about how we ought to deal with Merck and what was going on and this and that. So we went in the next morning, and I talked for about an hour and a half to Maurice Hilleman, who's now retired, who was the infamous V.P. of vaccine development at Merck, and a number of the other people.

Hughes: Why infamous?

Rosenberg: He was infamous for having an incredibly foul mouth, which he demonstrated several times during my talk and subsequent talks, and for being incredibly tough-minded and incredibly productive. He's really the person who made Merck the best vaccine maker in the world, at least at that time. Ed Skolnick, who's now president of Merck research, had just arrived there.

[Tape 1, Side B]

Rosenberg: We had a lot of arguments about whether we had really improved expression or not, and did their assays go along with our assays and this and that, All we knew how to do at that point was manipulate yeast. We didn't know anything about how you grew large amounts of it. We didn't even have a fermenter, I don't think at that point. We were doing everything in flasks.

Competition from Genentech and Amgen

Rosenberg: What was really funny was we thought we had reasonably good discussions. But one of the discussions focused on-- Well, Genentech had been talking to Merck, and they came with this vial which they said had some very large amount of hepatitis B surface antigen which they'd purified from yeast, and they wouldn't let the people from Merck test it. They said, "Here's the vial; it's got some liquid in it. There's five milligrams of hepatitis B surface antigen in there, and we'll sell you the process for 50 million dollars," or whatever the number was. It was a lot of money.

I remember having this discussion about, well, what did the liquid look like? If it had that much surface antigen in it, it should have been foamy--did it foam? Here are all of these highly paid scientists trying to figure out what was in the vial--like it was magic, what was in there--and were the people at Genentech really telling the truth--or not. And I'll tell the subsequent outcome.

We finished our discussions--this was one or two in the afternoon–and we walked out. There in the parking lot, as we were leaving Merck, we ran into George Rathmann, the CEO of Amgen, who was coming to try and sell Merck exactly the same thing! And this is the George Rathmann who I had sent my resume to when Chiron was going to be part of Amgen. So that was really funny. We just said, this is ridiculous! We'd better get back to work.

Well, it turned out that that vial had come from Dave Estell at Genentech who was the first protein chemist there. He's now the head of research at Genencor. A number of years later--I had run into Dave a number of times before--having both drunk a large amount of beer at a Gordon [Research] Conference in New Hampshire one summer, we got around to talking about this stuff. He said, yes, there really was that much hepatitis B surface antigen in there–-"because I purified it, and I know it!" The marketing people at Genentech had a reputation for being very, very tough and pushy and just pushed too hard in terms of not letting Merck have any idea of whether Genentech really had a process for making this stuff or not. And so Genentech probably was ahead of us at one level, but Merck had already invested so much time and effort into how to purify the material from the strains and process that we had developed that I think it was just too late for them to change.

Hughes: Do you think Merck considered changing to Genentech?

Rosenberg: Oh, I'm sure they considered it.

Confounding Yeast Colonies

Rosenberg: It got even more amusing at one point--we had this contradiction between our results and Merck's results. We had developed a strain which we were sure was three- or four-fold better at making this stuff than Merck's. And we had sent them the yeast colonies on a plate. We said, "Here are the old colonies; here are the new ones." They said, "There's no difference between the old stuff we were doing and your new strain." We tested it here and we said--"Ours is three-fold better." And we went back and forth.

Well, we don't know this for sure, but we think this is what happened: At some point earlier on, Merck had accidentally started using our better strain in their fermentations. So yes, there was no difference because they were comparing the two new strains, not the new and the old. That ended up leading to a lot of teeth-gnashing and hair-pulling at Merck, because they probably ended up because of that having to pay us a higher royalty than they would have otherwise.

Hughes: Yet the royalty wasn't all that great.

Rosenberg: The royalty was not all that great. Because the situation was so competitive and we were such a young company, we really didn't have any leverage with Merck over our competitors, except perhaps in the patent arena, and I don't think the hepatitis B patents have completely sorted out. Biogen also was working on it, and they ended up essentially copying what we did. But they had some early patents on the genome of

hepatitis B virus from Pierre Tiollais's group at the Pasteur [Institute]. They ended up selling their process to SmithKline, and SmithKline and Merck basically split the market. But Biogen got a much better royalty than we did.

Contracts and Intellectual Property: Bill Green, Tom Sanders, and Bertram Roland

Hughes: Who was negotiating these contracts, the legal aspects of these endeavors?

Rosenberg: Probably [William G.] Bill Green, who's the head of legal now at Chiron. He was the original attorney who incorporated the company. He was a neighbor of Ed Penhoet's in the Claremont district in Berkeley, almost all of which burned down in the fire last year. But Ed's house didn't.

Hughes: Was he a consultant?

Rosenberg: Bill was a partner at Brobeck.

Hughes: He wasn't a full-time employee at Chiron?

Rosenberg: No. We ended up paying Brobeck an awful lot of money over the years until we finally realized that we could get Bill Green doing Chiron business. But we were paying what Brobeck charged its hours at, and we could pay him a lot of money and still save ourselves a lot of money, which is what we ended up doing.

Hughes: So he eventually did become full time at Chiron?

Rosenberg: Yes. He is now whatever the head of legal is called General Counsel.

Hughes: In 1983 Tom Sanders was hired.

Rosenberg: Yes. Tom had been a graduate student with Bill at University of Washington at the same time Ed was there. Maybe he was in Champaign-Urbana for a little while and had then gone to Princeton as an assistant professor, and the department that he was in there was in the process of falling apart. It had some really superb people, a number of whom ended up at UCSF--Bruce Alberts, a number of other people. Tom's still at Chiron. He's a jack-of-all-trades in terms of patents, business development, being a gofer running around doing all of the nonscientific things that needed to be done.

I think Bill Rutter did the negotiating, to tell you the truth. But Tom did a lot of the other logistical stuff.

Rosenberg: Why don't we stop for a second, because I want to go check an experiment in the lab. [tape interruption]

Hughes: We were talking about Tom Sanders.

Rosenberg: So Tom was sort of the jack-of-all-trades and probably master of none. Chain smokes. Totally hyper. Very bright. His office makes my office seem like everything's in one place. And he just did a lot of things that no one else had any clue how to do. Like we didn't know anything about patents. He tried to get people to keep notebooks that would be relatively legally binding documents. It was impossible, because no one had ever done that before, and no one wanted to do it. They just wanted to do experiments.

Hughes: Did he come knowing that sort of thing, or did he have to find out?

Rosenberg: He picked it up.

We had an outside patent attorney at that point named Bert[ram] Roland, who was well known because he wrote the Cohen-Boyer patent [applications]. But his patents were totally incomprehensible. The scientists who were the inventors could not understand what he was talking about. You would get these drafts back, and it would take days to figure out what he was saying--even though we were the inventors; you would think we would understand it.

Hughes: Was it the legalese?

Rosenberg: Yes, it was the legalese. The whole question with patents is how broad claims you can get. You can always get very narrowly defined things [claims]. Like if you did exactly this and no one has ever done it before, you can probably get a patent on it. But unless whatever that is happens to be incredibly valuable, the patent, at least in what we were doing, isn't all that important. What is important is, can you say this is an example of how to do something and to someone skilled in the art it's obvious that you could do all these other things too, based on this initial discovery.

So the whole game with the patents, especially in the early days in biotechnology, was how broad coverage could you get. Like, could you get a patent on expressing any non-yeast protein in yeast? Well, that would be a pretty good patent. You were always trying to play games with trying to improve the breadth of your claim. I think the way Bert looked at it was, he would write cases [applications] that were so long and incomprehensible that the patent examiners would just give up and give him all the claims. I think that probably happened a few times.

Hughes: But the whole field of patenting in biotechnology was ill-defined at that stage--

Rosenberg: It still is to some extent.

Let me look at the chronology again. Dino started in June of '82--that's about right. So our meeting with Merck must have been shortly thereafter--sometime in the summer of '82.

Martin Marietta and Protein Engineering

Rosenberg: One of the things that happened around that time was we were running out of money. We had the money from Merck. But we were adding people pretty rapidly, and we were not publicly held. As a matter of fact, I think at some point in the spring to summer of '82, for at least one or two months, Ed Penhoet and C.K. paid the payroll out of their own pockets. I don't know if they'll ever admit that, but I'm pretty sure it's true.

Martin Marietta, a big aerospace company, had at that point made some investment in Genex. I think that was around the same time. They thought they were going to do protein engineering. Well, nobody knew how to do protein engineering.

Hughes: Why was Martin Marietta--

Rosenberg: --interested in protein engineering? I don't remember, but I'm sure Ed and Bill know. They decided that they wanted to make some investments in biotechnology. I think Bill had known one of the people. Martin Marietta at that point was running the Oak Ridge National Labs in Tennessee, where a lot of the early atom bomb work was done, purifying U[ranium]-235. But they also had quite a big biology program, which originally came out of radiation biology. Bill had been a consultant to the board there or something and so had met one of the guys who was head of research at Martin Marietta who actually subsequently was on Chiron's board for a number of years--whose name I'm blanking on. Somewhere along the line through that connection, Martin Marietta bought x percent of Chiron stock in a private placement, and we got $5 million dollars or something out of it.

Novo Nordisk and Factor VIII

Rosenberg: Around the same time we--actually according to this chronology it was a bit earlier [January 1982]--we had signed a contract with Nordisk to work on factor VIII. And that was a big project.

Hughes: Why factor VIII? How do these projects arise?

Rosenberg: There were a few projects where it was obvious that if you had a cheap way of making the protein which you knew was the active constituent that it would be a product because they already were products. But the proteins were coming from natural sources. The best example is insulin, which Chiron also worked on with Novo Nordisk. As a matter of fact, all the human insulin that's now sold by Novo Nordisk uses the process that was developed at Chiron. So insulin is the best example.

Factor VIII, which is the protein that's missing in hemophiliacs, was the other example. It was made from blood products. It was very impure. Even though we didn't know anything about HIV, it was clear hemophiliacs got hepatitis B--they got lots of diseases because of the way factor VIII was made. People pooled lots and lots of blood from lots and lots of donors, and then they fractionated the blood, and one fraction was the

fraction that contained factor VIII. Well, it was very impure; it might have been one part factor VIII in a hundred thousand. The economics of the blood fractionation industry were driven by the fact that you could get factor VIII out, and you could prevent hemophiliacs from dying of bleeding.

Hughes: So these proteins were obvious targets, is what you're saying.

Rosenberg: It was obvious that if you could make the protein, it was a product. It was true of the insulin; it was true of factor VIII. It wasn't true of a lot of other things. Every biotech company was working on those obvious proteins.

Hughes: Why would Chiron, a young company, think that it could possibly compete?

Rosenberg: Well, for two reasons. We had what we thought were some of the best people in the world at cloning and expressing genes. And we also at that point in our career were willing to work on any project that someone was willing to pay us for where we thought our technology was going to give us an advantage.

Hughes: It was either that or not work, wasn't it?

Rosenberg: It was either that or not work. And so we did a lot of what we called recombinant DNA service work, contract research at that point, even on projects we weren't that interested in. Well, what we tried to do and what we actually did do was to retain the technology. We never sold technology. If someone wanted us to work on factor VIII, we said, "What you'll get out of this is a process for making factor VIII, but that's all you can use it for. You can't use it for making other proteins; you can't use it for this; you can't use it for that.

Hughes: There's a contract with a Belgian company [Petrofina Group] to make enzymes.

Rosenberg: Yes, that's much later. Actually I was the head of that project. I know that one pretty well. That wasn't until '86. Let me go turn off something in the lab. I should probably stop.

Research on Factor VIII

Problems to Solve

[Interview 2: October 1, 1992] [Tape 2, Side A]

Hughes: Dr. Rosenberg, we were talking last time about factor VIII. Would you say something about the problems that you encountered?

Rosenberg: Yes. Early on I didn't have a lot to do with the project. Most of my involvement was in the '84-'85 time frame when we already had the gene cloned and we were trying to express the protein, which presented some of its own difficulties.

The initial problems were that no one knew where in the body factor VIII was made. People knew it was present in the bloodstream in very small amounts, complexed with another molecule called von Willebrand's factor. But nobody knew what its site of synthesis was. Some people thought it was the liver, some people thought it was endothelial cells.

But it was also clear that it was made in very tiny amounts. So it posed a real difficult problem as to how to pull out the gene. What people usually did at that time was to find a tissue source or a cell line that made large amounts of the protein of interest, and then they would make cDNA libraries from that, and then from partial sequences of the protein make nucleotide probes which were complementary to the cDNA. Then you could hybridize those and pull out clones for the right thing, at least in theory.

We had two problems. One was, we didn't know where the protein was made, and secondly, no one had isolated the protein in a pure form. So we didn't know what portions of the protein--it was clearly a complex molecule--were really factor VIII. It turns out it's actually present in a number of different forms. It's made as a large precursor, which then gets chopped up into a number of different pieces, some of the cleavages activate the molecule, and some of which then inactivate the molecule. So it's sort of a cascade effect over time, where you increase activity and then modulate it--you don't want too much coagulation, and you don't want it there forever.

The work went on on two fronts. The initial part of the work, the '82-'83 time frame, was largely involved in trying to isolate enough of the protein itself and to identify what really was the protein. That was work that George Kuo, Martha Truett, and Frank Masiarz at Chiron were involved in, in very close collaboration with the people at Nordisk who had a lot of experience working with the protein and provided a lot of the assays for it.

We still weren't sure at that point what the constituents were, but we had some isolated proteins which we could make probes from. They didn't correspond to any other known proteins, so it was as good a guess as any. Coagulation activity in a test tube assay correlated with these proteins--it didn't prove those proteins were required, but at least it correlated the right way. But we still didn't know what tissue it was made in. So we decided to take a strategy where we tried to clone directly from the genomic copies of the gene. So instead of making cDNA, which is copies of the RNA, we went directly for the gene.

Hughes: How would that help?

Rosenberg: Well, we didn't need to know what tissue it's from. The DNA in every cell in the body is the same; what's expressed is different. So we had genomic human libraries, and we went after those. That actually turned out to be an initially successful strategy, because it turns out there is one quite large exon, quite large piece of expressed protein, in factor VIII that's contiguous. It turns out it's a huge gene--the gene is 300 kilobases, 300,000 base pairs. And the coding sequence is only about nine kilobases.

Hughes: Did you know any of this before you started?

Rosenberg: No.

Hughes: Chiron was working all this out?

Rosenberg: Yes. We knew Genentech was very close. We heard rumors. Genetics Institute was close. We knew it was a battle. We were as usual keeping pretty quiet and everyone else was getting all the publicity. That's the way it usually worked.

Hughes: Was that the strategy?

Rosenberg: I don't know if it was strategy or not. It used to piss everyone off. [laughs] Especially with the hepatitis B vaccine where we knew we were two years ahead of anybody else, and yet everyone else was getting lots of press. But we beat them to the marketplace anyway, thanks to Merck in large part. But that's an aside.

The Research Sequence

Rosenberg: Quite early on we were able to fish out a part of the gene with these oligonucleotide probes. Once we had a piece of the gene, it became easy to figure out where material was made and then to get the rest of the cDNA. It turned out still to be very difficult because the cDNA itself was nine or ten thousand bases long, and cloning cDNAs that large was quite difficult, on top of which it was very rare.

Daniel [Caput], a Frenchman working here at the time--he now works for Sanofi in France--ended up eventually cloning the whole cDNA in two pieces. Having that first piece of the gene which ends up encoding a good chunk of the active form of factor VIII will probably turn out to give us quite a good patent position in the whole business. We probably had that as early or earlier than anyone else. Some of the early work in the protein arena had defined quite well at least one piece of factor VIII required for activity. It turns out the active form is two chains that are derived from the same gene that get clipped out but still associate.

Protein Expression

Rosenberg: I got involved in the project after we had the cDNA clone in trying to express the molecule, in trying to make functional factor VIII, either in mammalian cells or in yeast. It turned out to be one of the most difficult molecules to make because it's very complicated. It's very large, and it's very susceptible to proteolysis, to being chopped up, whether appropriately or inappropriately. We worked out a number of strategies around that and actually almost accidentally ended up getting one very good cell line for the whole full-length material. We later worked out a strategy where we could express the two halves separately, and they would form a complex together and make the active

molecule. That turns out to be much easier. If it turns out to be a commercial process, it will be the way Novo Nordisk, previously Nordisk, will make the molecule.

Hughes: Do you know in advance the system in which a protein is best expressed? Wasn't it hepatitis B that was not expressible in *E. coli?*

Rosenberg: Well, we've been learning over the last decade.

Hughes: Is it trial and error?

Rosenberg: A large part of it is empirical. I think it's much easier to tell now. If you gave me a protein sequence now and said, "Where should we express this," I could much more easily tell you where we shouldn't express it than where we should.

Hughes: Based on what kind of information?

Rosenberg: Based on a number of factors having to do with how the molecules are put together. Some proteins are very highly cross-linked, and that turns out to be something that bacteria don't do very well, except if you put the molecule into a specific compartment. You can take one strategy, which is to say okay, the molecule's not going to be folded properly when I make it, but I can re-fold it in the test tube. That's difficult but doable, and some people are very successful at that sort of strategy. We'd rather have the organism fold the molecule for us, if possible.

With factor VIII, well, we knew it was made in mammalian cells, so that's what your fallback position was. But that turns out not to always be the case. There are some molecules that get caught up in the cell because they have to go through different environments within the cell before they get secreted into the medium, which is usually what you want to do. And sometimes they get caught.

Hughes: Chiron had started with a yeast expression system. By 1984, '85 you had mammalian cell culture systems in place?

Rosenberg: We had the beginnings of it. I think it really started around that time with factor VIII. [short pause]

Retaining the Technology

Rosenberg: That's a good point: One of the things that we often found in working with other companies was that we developed new technology that they paid for. We always kept the technology; they got a process, for making factor VIII in this case. We had developed a series of expression [vectors] that we hoped would be generic--we could use them for any protein.

Around that time we and a number of other groups realized that some of the signals that are used in some of the herpes viruses were very potent for expressing proteins in

mammalian cells, and we incorporated one of them into the factor VIII expression [system].

Hughes: So the contract is carefully written so that the contractor gets the product and not the process.

Rosenberg: Well, they get the process for that particular protein.

Hughes: So they can't apply it to other proteins?

Rosenberg: Not without giving us royalties on the other products.

Hughes: Wouldn't that be the way that any biotech company would set up its contracts?

Rosenberg: Yes, I think so. Those were the crown jewels. At that point what people didn't know how to do well was express proteins. We were pretty good at it. We still had problems occasionally.

Early Targets in Biotechnology

Hughes: Who were your competitors in protein expression?

Rosenberg: Well, essentially all of the biotech companies. That's what biotechnology was founded on. Cloning DNA, per se, was enabling, but the real business, what you sold were proteins.

Hughes: It didn't do much good to clone it if you couldn't express it.

Rosenberg: Right--except for diagnostics and things like that. But the products of biotechnology are proteins, and so what you did was to manipulate the DNA so you could express the protein.

Hughes: What gave one company an edge over another if they were trying to do essentially the same things?

Rosenberg: I would say that there were two differences. One was focus. It really was serendipity as to which proteins people focused on early on. Genentech focused on human growth hormone and tPA [tissue plasminogen activator]. Human growth hormone you can make in *E. coli* by the bucketful--works fine. When Genentech initially made it, it had an extra methionine on the end terminus, and no one really knows whether that matters or not. There's a lot of debate. tPA is very hard to make in anything except mammalian cells. So Genentech focused very much on bacterial expression and mammalian cells.

Yeast Expression Systems

Rosenberg: The first proteins we worked on were hepatitis B surface antigen particles and EGF--epidermal growth factor. You could make EGF in modest amounts in *E. coli.* Actually, Burroughs Wellcome in England had originally made EGF in *E. coli* reasonably well, but we weren't very good at it. When Tony Brake figured out how to use the yeast alpha factor secretion system, the first gene we put in front of it was EGF, and it worked beautifully. It put it in the medium, it was active, it made lots.

I still remember that day. Doris Coit who was working with Pablo had just done a radioimmunoassay, and she was walking down the hall with this paper shaking her head. I looked at her and I said, "Doris, what's wrong?" She said, "It's the same amount as the control." I said, "You're kidding." That's five milligrams per liter! That was tons! We couldn't believe it. That was probably '82 or '83.

So our focus serendipitously really was yeast, because the first couple of proteins we worked on, worked well in yeast. So there was momentum to keep working in yeast. We started getting a few fermenters here and there. That was later on probably, and we began getting people who were interested in yeast. So there began to be a nucleus or critical mass of people who were thinking about expressing proteins in yeast and manipulating yeast so they would express proteins better.

Hughes: What about other companies? How many were using yeast expression systems?

Rosenberg: Not very many. Genentech had a yeast group early on, but I think they never had the right protein to work on. They were working on hepatitis B, but we were probably working on that earlier than they were. Zymogenetics, which is now a part of Novo Nordisk--it used to be called Zymos--had an early yeast program and a very good one. But that company never seemed to make the breakthrough out of being a research group and expanding into manufacturing. A number of companies had early yeast groups. Collaborative Research in Boston had a yeast group early on that was quite good. But none of them made the commitment early on that they were really going to manufacture proteins in yeast. It just fit in with our plans to do that. And that's what happened.

The mammalian cell culture expertise really developed through factor VIII, also through some of the work on the herpes proteins--the program that Rae Lynn Burke started and still directs--where it was clear that you had to make those proteins in mammalian cells for them to fold properly, even in some cases it's difficult there. So we sort of learned that as we went along. Around ‘84, ‘85, we also had a program with Behringwerke, which is part of Hoechst, to work on tPA, and I guess I was part of that before I was part of factor VIII, now that I think about it. Let's look in the notebooks.

Contract Research

Hughes: Why did you move from one product to another?

Rosenberg: We were hit men! [laughter]

Hughes: Is it because you're good at expression? So when a project came to that point you were called in?

Rosenberg: Yes. Well, early on, Chiron's initial strategy to a large extent was, we had an expertise that not many people had, and one of the ways of supporting the research here was to have other companies come to us and say, "We'd like you to make this molecule. Can you do it?" Bill Rutter would always say, "Yes." He would never ask us, and then we'd have to do it! He was usually right, although we weren't sure a lot of the times. Very early on Chiron had very little in-house research that was focused on its own projects.

Significance of Hepatitis C for Chiron

Hughes: Hepatitis B was about it, wasn't it?

Rosenberg: Well, hepatitis B was funded by Merck.

Hughes: I think of it as being brought from UCSF.

Rosenberg: That's true, but it was funded by Merck there as well.

Hepatitis C was really the major project that we had early on, probably from '83 or '84, that Bill was really willing to commit our own resources to and pay for with our own money. Even though he knew it was a long shot, he thought it would be a home run if we managed to hit it.

Hughes: Which you did.

Rosenberg: Which we did! Well, three or four years later.

Hughes: If you had to pick one thing that Chiron is known for, would it be the characterization and cloning of the hepatitis C virus?

Rosenberg: Yes, I think that's true. That's what made the company a success--maybe the transition from it being a losing proposition, though a very good research institution, to a company that was going to be both profitable and successful. That was the key.

Hughes: So you're saying that not so much because of the scientific achievement, which it certainly was, but because you now had a really marketable product?

Rosenberg: I think both: It was a really world-class scientific achievement.

Hughes: Which helped of course in the marketing end of things.

Rosenberg: Yes, it certainly helped--and the fact that we beat everybody else that had been working on it for longer than we had. But the key thing from the company's perspective was that

this immediately gave us a dominant position in part of the major segment of the blood-screening market. This was the first time, at least that I'm aware of, that an infectious organism had been discovered in a company. It had never happened before. So there were all these interesting proprietary issues: "Well, does Chiron own this virus?" And it was serendipitous that there was already hepatitis A and hepatitis B, so it became hepatitis C, for Chiron of course.

Hughes: [laughs] That's why you went after it, of course!

Rosenberg: But that was clearly the major event in terms of changing the nature of the company. Before that, there was a good chance that Chiron would have become acquired by a major company, because even though we had lots of interesting research, there was no relatively short-term path to making us profitable. And it was going to depend upon the vagaries of the public financing markets as to how much money we could raise and how long we could go without selling more and more equity to partners. That achievement really gave us independence.

Acquisition of Cetus and Its Effects

Hughes: Was the threat of acquisition hanging over people's heads in the early days?

Rosenberg: I'm sure it was, but we didn't think about it a lot; we were too busy. I'm sure Bill thought about it.

Hughes: Reflecting on Roche's acquisition of Genentech, Dr. Valenzuela said that if that ever happened to Chiron, he would leave. Is that a common sentiment? Acquisition would mean a lot of brain drain?

Rosenberg: Well, I think we saw it in a different way with the merger with Cetus. We saw a substantial brain drain from the Cetus side, which perhaps one would expect, but also from the Chiron side, which I think was a little less expected.

Hughes: Why would that be?

Rosenberg: Well, first of all, Chiron went from a company of about 700 people, say eighteen months ago. We acquired four companies last year on three continents, and now it's a company of 1700 people, and it's a very different place. Ninety percent of it used to be in Emeryville, and if you wanted to go talk to Bill or Ed or Pablo, it was no problem. They might be out of town, but you could get hold of them without much difficulty.

Then all of a sudden Chiron became a multinational corporation, which is what it is now. It's a pretty big company, and so it's a very different place. There were quite a number of fairly senior people at Cetus in the research organization, as well as people at Chiron who had been here from early on, let's say who came in the '81 to '83 time frame, so they'd been here close to ten years or longer. Well, there weren't that many positions of substantial responsibility for all those people.

So it became a question of people looking at this and saying, "What kind of job do I want? How much responsibility will I get here? How many slots are there at the level that I want to be at?" And balance that with the fact that they were getting calls from headhunters twice a week, offering them three times as much money, or three times as many people, and positions in start-ups where they would be directing research and things like that, and you have a lot of entrepreneurial people, plus a lot of the people were around forty, and they were ripe for a change. I think we'll probably lose a few more people over time.

Chiron Organization

Internal Businesses

Hughes: It's a chronic problem with practically any corporation you name. Often it starts out with a small core group sharing the same philosophy and an intimate set of conditions, and then if you're successful, you get this huge structure which is necessary for the evolution of the company but makes it a very different thing.

Rosenberg: Yes, and the question becomes how you evolve the company so you can balance relatively small units that are human-sized so people feel like they're an important part of something. So you need to break the company up into units, and yet that will by definition require some redundancy. Of course, you'll have people doing similar jobs within similar units. You could say, "Well, we need to centralize all that stuff." But if you do that it becomes inefficient. So you have to accept redundancy to keep innovation alive. I really think that's true.

Scientists as Managers

Rosenberg: Chiron has always been very good at that. It has generated, internally, a lot of different businesses. Some of it by in-house research, others by acquisition. But it's very much a multiheaded hydra of a company that has its fingers in lots of different pots and that, I think, has kept it interesting for people.

Hughes: What difference has it made that the superstructure remains essentially scientific rather than managerial?

Rosenberg: Well, I think it's more specific than that. The people who started the company still run it, and that's obviously provided a tremendous amount of continuity. It has never been ambiguous about who you needed to talk to if you wanted to get something done.

Hughes: Do the scientists at the top appreciate the need for a certain redundancy which maybe a business-type would reject?

Rosenberg: I don't know if they appreciate it or not. It clearly evolved that way, and they were at least prescient enough not to interfere with it. Now I think that was in part probably because they were so busy with everything else, that it just sort of evolved. Chiron has always had a chaotic organizational structure, and that is both a blessing and a curse. It means it's often difficult to figure out how to get things done, and there never seems to be a final decision on anything. So things are very fluid, and it's sometimes hard to get commitments for resources to do something until it's so obvious that you are behind where you ought to be.

Hughes: And that's because there isn't the key person to go to to make the decision?

Rosenberg: Well, Bill is both a scientific leader of the company, and has been certainly since its inception, and also the strategic business leader. So he wears two hats now and can't always be on top of both things.

One key thing is that when something important scientifically comes up, you don't have a hard time convincing the powers that be; they understand what you're talking about. It's real obvious. You get good questions at meetings, and that's really key to keeping people interested in working here on a scientific level. There also is another side which is that people--nonscientific people--who traditionally have more powerful roles in the company I think feel like there's this inside track for technical people. I think that's probably true.

Hughes: Is that one reason there has been a turnover of the managerial people at the top?

Rosenberg: Well, I think it's a combination of things. I think there's the perennial problem in any company that goes from being a start-up to being a larger company: Do the founders really have any experience to run the company later on? I think Bill and Ed have always kept their own vision of things and probably haven't given as much freedom to people who would otherwise have a lot of latitude. In contrast to the research side of the company, there has been a tremendously fluid succession of people in nonscientific managerial positions, some of whom are very good; some of whom probably weren't so good. All, I think, felt like they never really were part of the inner circle.

Hughes: Is the problem related to the two hats Dr. Rutter is wearing?

Rosenberg: Well, Ed played a major role in negotiations with partners and in dealing with the investment community. Much more so than Bill. Bill dealt more, at least in my impression, with strategic issues.

[Tape 2, Side B]

Rosenberg: When you take away the strategic and scientific scope of what I perceive as Bill's job--dealing with partners and the investment community is largely what Ed focuses his time on--there's not a lot left for someone who's used to having a major role in corporate decision-making.

Hughes: I imagine that was a real problem.

Rosenberg: And I think it has always been a problem. And plus the anarchic, chaotic nature of the company as a whole I think tended to drive people crazy who were used to more easily perceived lines of communication and authority, and just cleaner structures--where it was easier to perceive how to get things done. So that's a big sidelight off into Chiron's present more than its past.

Opportunism and Serendipity

Hughes: Has Chiron in recent years had a fairly stable idea of the niches in the biotech world that it wanted to fill?

Rosenberg: I think that's true. A lot of it was also opportunism and serendipity. You always have to bear those in mind because you don't know how things will turn out. If all of a sudden you figure out a better way than anybody else has to make small peptide hormones, well, you're going to think seriously about getting into the business of small peptide hormones. That's exactly what happened at Chiron, and that's why we're interested in EGF and IGF-1, PDGF, and insulin.

Notwithstanding prior interest in the diabetes area from Bill's earlier history, the fact that we had this yeast system that enabled us to make those molecules in a facile manner made it possible for us to think about being in that area. And so it's really technology that drives what businesses you get in. And you just have to be opportunistic about what turns up to work well.

Chiron's Vaccine Business and Further Thoughts on Project Selection

Hughes: I get an impression of a firmer set of categories within which Chiron was working from the annual reports. What about the concentration in vaccines?

Rosenberg: That derived from the fact that from the early work on hepatitis B, we had a reputation that said we can make vaccines--or couldn't make vaccines; we could make proteins in yeast, which turns out for almost every other vaccine is not useful. Every other vaccine we're making now with one exception is made in mammalian cells. But having had this initial success working with Merck in getting the recombinant hepatitis B vaccine, we could then go talk to Ciba-Geigy with some credibility and set up the joint venture, and that's really where that came about.

Hughes: So it really isn't that it was all carefully thought out in advance. Things evolved--

Rosenberg: Well, I don't know; you'll have to ask Bill. Maybe he had it all carefully thought out in advance. But things definitely evolved over time, and the directions the company took were based largely on what worked well. The twists and turns and changes of direction were really driven by a number of factors, but probably the first one was what worked

in the lab, and what did we think we could then develop into a process that might be commercial.

Before we were working on factor VIII, we had a contract with Behringwerke, part of Hoechst, to work on tPA. Genentech was "n" years ahead of us, where "n" was probably two, but we actually learned a fair amount about mammalian cell expression through that project, which actually turned out to be quite useful in factor VIII.

Chiron's Work on tPA

Rosenberg: One of the reasons that I ended up working on factor VIII was because I'd worked on tPA. Even though I didn't know anything about mammalian cell expression except in theory, the theory turned out to be somewhat useful. We ended up making a number of tPA derivatives which had potentially some better properties than tPA itself, which I don't think we'll ever get commercialized because the patent situation then wasn't clear. It's pretty clear now that Genentech will have a quite dominant position on tPA, and tPA turns out not to be that good a drug anyway! [laughs] Which is a disappointment for Genentech, I think.

Hughes: So what has happened to that research?

Rosenberg: I don't really know to tell you the truth. We've published a couple of nice papers on it. My guess is that Hoechst is not following that up in any significant way. But we developed a good relationship. We did a pretty good job in the protein engineering end of things, and what it enabled us to do was develop a good relationship with the people there, so that when there were other projects we might want to collaborate on in the future, we knew the people who were high up in the organization. We could talk to them, we had some credibility with them, and so that became very important in later developing business deals that were less one-sided.

Academic Research; Commercial Development

Hughes: Does the academic world regard the science that comes out of industry with the same credibility as it would out of academia?

Rosenberg: You should probably ask an academician. [laughter] Well, it's different at some level. We certainly collaborate a lot with academicians. I think Chiron has been somewhat unique in the sense that to a large extent, with a few marked exceptions, it has been a development company. Chiron has not particularly been a research company. We've done applied research, the research being how do you use what we know about organisms to express other proteins in them. We haven't done the basic biology on those organisms, except where are they [located].

People in academia oftentimes discover proteins, but they don't know how to make them into products. We know how to make them into products. And in order to investigate the biology further, you need to have large amounts of these proteins to be able to make them in a functional form, to be able to purify and characterize them. So then what you find is that someone in academia will make a discovery, we'll collaborate with them to make large amounts of the proteins in functional form, and then they can then use those proteins collaboratively with us to try and understand more about the biology, to see is there a possible therapeutic use of the protein? So that works quite well, and we have lots of collaborations.

In the area of protein structure-function, which is a pet interest of my own, the technology to be able to make these proteins in heterologous organisms in large amounts has enabled protein engineering, as it's called, to get its start to a large extent within companies. More so than in academia.

The technology to make the proteins started mostly in the companies. For people who are sort of physical biochemists who are interested in protein structure, this technology has revolutionized that area of research. I have lots of collaborations with people in that area because that's something I know how to do. So that I think is quite a good relationship. It's also a good relationship in the sense that because of the present funding situation, having a biotechnology industry has created a job market for a lot of people which wouldn't be there otherwise! So that's I think quite--

Hughes: Many scientists in the biotech industry have come from academia where, as you just said, the emphasis is on basic science--

Rosenberg: Teaching as well.

Hughes: Yes, while in industry the emphasis is on the product. Was that change difficult for you?

Rosenberg: [long pause] I don't know. I think that's something that evolves. There are different kinds of scientists. There are scientists who are only interested in asking interesting questions and answering them. And along those lines, there are scientists who end up spending their whole scientific career working in one small area and creating a cathedral of knowledge about that system, which is wonderful, some of the most beautiful work that gets done.

You have another category of people who don't have the patience or the inclination to do that, where--as I say of a lot of people--they get bored every five years and then want to work on something new. I guess I put myself in that category, and I think a lot of people who end up in industry find that that mind set and industry fit pretty well.

The other side of it really is that most of the training that everyone got was funded by the National Institutes of Health whose charter is supposed to help the national health. And what better way to do that than to develop new pharmaceuticals that are going to be useful. So one doesn't have any problem rationalizing from a moral or ethical point of view doing this sort of work. Your goal is to cure disease, to treat disease, to diagnose disease, and I don't know if it's better than being a physician, but it's comparable. And maybe you can have more impact in the long run. So certainly there is no moral

quandary involved. You can get fairly wealthy at it besides, which I guess doesn't hurt.

Mechanisms for Collaboration Between Academia and Industry

Rosenberg: The difficulty at one level is, if you have everybody applying things, who's left to teach the next generation of scientists how to do research to work in either academia or industry? And that's a real problem especially given the budget difficulties these days. What you're seeing now, and you'll see it increase, is that you will find industry funding research and training people in academia. Chiron is already part of biotechnology training grants--one with UC Davis, and there are a number of other training grants along these lines, part of a joint grant with some people at UCSF.

Hughes: Does that mean that Chiron people work at the university?

Rosenberg: A number of people have joint appointments, adjunct professorships in a variety of institutions. With this program at Davis, which is really just getting started, there will be graduate students coming and spending part of their time training here. I have a lot of close ties with people at Berkeley, collaborative ties there. In the Bay Area in particular--and I think it's probably true in Boston as well--there are close ties between the academic and industrial communities, largely because the first generation of scientists in the biotech industry came out of there. And it clearly is beneficial to both sides.

To get back to Chiron's evolution: The turning point was probably in the '86-'87 time frame when it wasn't clear where the company was going to go. We had--probably in early '87--gotten our first clones of hepatitis C. We still weren't sure they were real, but we were pretty sure, and that became surer and surer as time went on. At that point we knew the company was going to be quite successful. And that marked a big change.

Turning Point: Chiron Moves Toward Corporate Integration

Rosenberg: That was when the company went from being largely a research-focused organization to a company that clearly had to develop other parts to make it fully integrated in some sense, even though a large part of the diagnostics business was being done in a joint venture with Ortho Diagnostics, which is part of J & J [Johnson & Johnson]. We had to figure out how to manufacture proteins, etc. We had to start dealing with the FDA in a serious way about getting protein products approved. At that point our pipeline was so full that the research effort at some level became almost secondary to development, quality issues and regulatory issues.

Hughes: Was everybody pulled into those issues?

Rosenberg: No, but a large number of people were. A lot of people who had started projects or followed them as they went on in development, and that left a bit of a gap at the research end of things. We were doing less and less contract recombinant DNA research at that point, partially because we were too busy doing other things, and partially because the technology had become a lot more spread out throughout the world, and it was less valuable per se.

Products: Disappointments and Possibilities

Rosenberg: We also had a few disappointments around that time in the therapeutic arena, around EGF which we had had in the [clinic].

Hughes: Am I right that EGF was the impetus for Chiron's entry into ophthalmics?

Rosenberg: Yes, absolutely. There was some good early evidence that in the growth factor area, both in wound healing and in ophthalmology in particular, that a number of different molecules, EGF [epidermal growth factor], fibroblast growth factor--FGF, and PDGF--platelet-derived growth factor might be useful either alone or in combination in healing a variety of wounds faster than they healed without them, or in fact ones that didn't heal at all.

The thought was that since with the eye you don't have a systemic delivery problem, it would be a good system to try them out. And we initially had some quite spectacular success. The problem was the clinical trials weren't very simple. We were looking at clinical nonhealing corneal defects. It turned out to be a very heterogeneous patient population, very hard to develop and do controlled studies because you couldn't get a matched population.

There were some problems with the formulations, so people were having pain when the growth factor was there. I don't know if it was ever figured out why it was. We changed the formulation and finally got rid of it. We were very excited about EGF early on. The same thing with superoxide dismutase, SOD, another protein which theoretically looks great and has turned out to be a bit of a disappointment in people. It looked great in all the animal studies, and you got it into people, and you couldn't see any real beneficial effect. It didn't do any harm, but there was no real benefit. So those things were disappointing.

But at the same time we had the hepatitis C stuff coming, and without that it would have been quite a demoralizing time. So the shift then was away from therapeutics into diagnostics and vaccines, and that's really been where for the last five years Chiron's major focus has been.

Protos, A Chiron Spinoff

Rosenberg: In 1988 or '89 Protos, which I was involved in, was started.

Hughes: [consulting chronology] '88

Rosenberg: I started in the beginning of '89. It was meant to focus on new ways of developing therapeutic agents and was looking off into the next century in terms of where products were going to come from.

Hughes: Whose vision was that?

Rosenberg: That was Bill's and Dan Santi's.

Hughes: Who's Dan Santi?

Rosenberg: He's a professor at UCSF in pharm chem [pharmaceutical chemistry] and biochem/ biophysics.

Hughes: Well, tell me about Protos.

Rosenberg: Protos was set up with the premise that recombinant DNA at least in part gave one not only the ability to make proteins as drugs but also to take specific proteins and use them as targets for drug discovery. So the proteins were no longer going to be the products; you would be able to use them to find novel molecules that would be. These would probably be like more traditional pharmaceutical products--smaller molecules might be orally available, etc. The notion was that given the ability to clone and express human proteins in large amounts, one could look very specifically at proteins which would be of therapeutic interest for particular indications based upon the real explosion in the molecular understanding of disease. The ability to make these targets, as they called them, was one part of the equation. Another part of the equation was the notion that you could use automation and robotics to generate large numbers of molecules synthetically. It was a technology that Dan thought was at its beginning and that might be possible to do. It was something that evolved here as a function of time.

The notion was that because you can make large amounts of proteins, you could use those proteins to select molecules out of mixtures with the protein that bound to them; you could find needles in haystacks, which you couldn't do any other way. That turns out to be difficult but doable. And finally there's just been such a rapid increase in the rate and cheapness of computational power that computational chemistry (or molecular modeling as it's perhaps more commonly known--or rational drug design as people sometimes call it these days) was becoming more and more important because you could do calculations in reasonable lengths of time now without having to buy a great supercomputer. We knew how to do the calculations before; we just couldn't do them; they'd take a year. Now they take two days. It’s gotten to the point where you can buy, at least for some kinds of computational problems, a computer for twenty thousand dollars that's one third the speed of a Cray that costs $15 million dollars.

The ability to make the proteins, the ability to select molecules out of mixtures, trying to use robotics to evaluate things, and a whole number of other technological innovations led to the notion that you could put these together and come up with new methods of increasing the rate at which you find novel pharmaceuticals. And that was what Protos was founded to do.

Protos was both good and bad. It pointed out some of the inefficiencies and difficulties that had developed within Chiron's structure as it grew, and it also caused probably more grief than it was worth. In some ways, it would have been better off either completely within Chiron as a separate department, though it perhaps never would have been as creative or attracted the kind of people it did as a start-up, or spun off as a completely separate company and let it survive on its own. The hybrid was very difficult to manage. It was set up as a separate company that Chiron had a controlling interest in that enabled us to attract a group of people who were much more chemically focused than the rest of Chiron was. It had both the blessing and curse of having its own identity and having a separate identity which enabled it to develop some very new things but also caused difficulties in its relationship with the parent. It was the adolescent for most of its life and rebelled a lot.

Hughes: It still exists?

Rosenberg: No. Last year after the merger with Cetus and after hiring Walter Moos, the present head of the Chemical Therapeutics Group, which is what Protos evolved into in part, it was re-merged into Chiron as this Division of Chemical Therapeutics, along with some other parts of the organization. At that point Chiron bought back the remaining shares, and it stopped being a separate company.

Hughes: Was that somewhat to obviate the problems that you mentioned?

Rosenberg: Yes. It just got to the point where instead of worrying about the scientific problems, we needed to face what focus we ought to have at Protos: What targets we ought to be working on, where we ought to be going, and how we should be improving the technology. We'd done a great job in developing the new technology; we hadn't really proved that it worked for anything. That's an important phase to go through in a technology-based company. You had to keep trying.

Determinants of Chiron's Priorities for Development

Hughes: Was the long development period a basis of the problem with Chiron?

Rosenberg: Sure. There was always at Chiron in the early days up through now and also in Protos this tension between keeping it at state-of-the-art technology and applying it through presently doable problems. People who want to do one don't want to do the other or aren't able to and vice-versa. There's always this sense that you've got Leonardo DaVincis developing the technology and the people in the trenches applying it.

It's very hard to have the right mix of people and prevent them from thinking one or the other is teacher's pet because you've got to give more resources to the people who are developing things because they're the ones who can get the products out the door. But you also have to give freedom to the people who are developing the technology so they keep doing neat things, so you'll be able to develop the products. It's very hard to balance and very hard to know.

That was one of the real tensions--what path do you follow? Where do all the minefields exist? Any technology-driven company has to face that as a problem going forward. When do you push the balance to one side or the other? Do you bring in technology from other places?

Up until the last four or five years, Chiron was always going to other companies and saying, "We're good at this. Do you want to help pay for development?" Well, now we have companies coming to us and saying, "We've got this new technology. Do you want to help fund us?" And there are reasons why it makes more sense for Chiron to do that now than to try to develop the research in house itself.

Another reflection of that is, the turnover in fairly senior research people in the last year or two has seeded a whole bunch of other companies which are doing new and interesting things. They'll undoubtedly come back to us because the people know us and they'll say, "Hey, we're doing this neat stuff. Do you want to help us fund development?" We've got enough money now to do that sort of thing. From Wall Street's point of view, it's much better for us to fund research for someone else, because that's an investment, as opposed to funding in house, because that's an expense. It means it's cheaper to fund things on the outside.

Hughes: It also means a certain loss of control.

Rosenberg: Yes. It also means you piss off your inside research people because they want to do everything themselves, and why are you funding these guys? We were always the people on the outside before, going to other companies whose research people would get pissed off and say, "Why are you taking money out of our budget to fund those guys--we can do it better."

Hughes: You have to stop.

Rosenberg: I've got to go in the lab.

Chiron's Forays in Ophthalmology

Allergan

[Interview 3: October 27, 1992] [Tape 3, Side A]

Rosenberg: Chiron tried to express EGF, and we'd had a little bit of success in bacteria. Searle in England was way ahead of us in that regard. Nevertheless we had had some contact with Allergan. Part of their business is in eye care. They sell contact lenses, for example. We thought there might be applications of EGF in healing wounds in the eye, so we had set up to go talk to them.

Right around that time Tony Brake had developed the yeast alpha-factor secretion system, and we had tried it on EGF as one of the first proteins we tried, and it just worked beautifully. We could make unlimited amounts of the protein, which was not at all the position we thought we were going to be in. So Ed Penhoet and I went down to Allergan and talked to them about EGF, feeling very full of ourselves, as opposed to coming with our hat in hand. Nothing ever came of that except some of the initial contacts with Bill Link, who was then at a company called American Medical Optics. It was a company he had founded that had gotten bought out by American Hospital Supply.

Chiron Ophthalmics

Rosenberg: Though those initial contacts with EGF is really the way Chiron Ophthalmics started. The subsequent history of EGF in ophthalmics has been a checkered one, but I think it's finally back on track. It's in the clinic again now, and I think probably under much more controlled circumstances. It's used now in corneal storage media. It turns out when you do corneal transplants, you don't always have someone you want to do the transplant on. The cornea is available mostly from people donating them upon their death. So it's important to be able to store them in a way that they are still viable. Chiron Ophthalmics--it's now called Chiron Interoptics--is the only company in the country that makes corneal storage media. And they use one with EGF in it because the cells are much more viable and they grow much better and keep much better that way. So it is being used now and we think it will be further used.

Hughes: But not in wound healing.

Rosenberg: Not in wound healing. But I think in the eye it will be used in wound healing eventually. There were problems with the initial clinical trials for a variety of reasons. It was never quite clear to me what the real reasons were but there were a number of problems with people having pain in their eye associated with EGF.

Growth Factors as Potential Products

The Oncogene Problem

Hughes: In an earlier session we talked about how so many of the early projects were being worked on by most of the biotech companies. Was this also true of EGF and the other growth factors?

Rosenberg: It wasn't as obvious with the growth factors as with some other products like insulin, that one being the paramount example, but also factor VIII. They were proteins that were already used as drugs. The problem was getting enough and having a recombinant source of the human protein, as opposed to using an animal source. One could make what seemed a compelling argument that the human protein ought to be better and that clearly you could replace the animal protein, porcine insulin, with human insulin. That has turned out to be true, though it has taken longer than people would have thought. There are occasionally people who tolerate porcine insulin better than human insulin and I don't think anyone really knows why.

Growth factors were much less well characterized as proteins in terms of their activities. They had been characterized in the lab but certainly not in people. There was also clearly some concern that these were proteins whose genes themselves or the genes for their receptors had fairly recently at that time been implicated as oncogenes. So people were worried that if you gave growth factors to people, you would give them cancer. And it's still a duality that's complicated with growth factors for topical use and things like that. They obviously play a key role in wound healing. At the same time if you have inappropriate expression of them, or over-expression of them or their receptors, they become oncogenes, because they're involved in cell growth. It makes very obvious sense. So it's a duality that has continuously been part of Chiron's thinking about growth factors. The pendulum has swung a bit. Now in my own research I think more about growth factor receptor antagonists and their possible roles in dealing with cancer, and perhaps also in other aspects where antagonists of these molecules may be useful.

Use in Wound Healing

Rosenberg: We also have quite a successful program now--it has taken a long time--with platelet-derived growth factor which is in phase III clinical trials by us and by a number of other groups and really appears to work in a number of kinds of wound healing.

One interesting sidelight to wound healing in general is that when you do clinical trials on people, you find out that people really heal pretty well, and then if you treat people aggressively in terms of healing wounds, they heal pretty well. So what you see is an incremental improvement in some of these factors, but it's rarely black and white. Then you get into cost-benefit analyses of okay, if someone has severe burns, well, you want them to heal as quickly as possible because they're at severe risk for infection which

could be life-threatening. But if you have people with bed sores, they are certainly going to be uncomfortable and they may eventually be a problem for them clinically. But in general--it's especially true in young people--they heal like that [snaps fingers]. It's clear that as we get older we don't heal as rapidly. So they are probably drugs for old people--old being over twenty. [laughter]

Wound healing is a very complicated area. There are multiple factors involved; there are multiple cell types involved. So it's complex trying to recapitulate what goes on normally. There are not obvious cases where there are deficits in this factor or that factor that you can point to and say, hey, someone is genetically deficient; this is their problem with wound healing. It's not like factor VIII and clotting, for example. There's probably a lot of redundancy in it, and so how you intervene clinically is complicated.

Growth factors are relatively safe so you end up doing a lot of your experiments in human clinical trials because you don't know where they'll fit in. It's very unlike developing traditional pharmaceuticals where you make a molecule for a specific purpose. But then your real problem is managing toxicity, and what you spend most of your human clinical trials finding out is what is the toxicity, what are the problems with the molecule. Protein is different. It's oftentimes the other way around. The toxicity is not a problem. It's what standard are you using for efficacy? So they [create] placebos in a lot of cases.

Insulin-like Growth Factor

Hughes: Do you want to comment on IGF?

Rosenberg: IGF has a lot of potential and it has probably been one of our less successful collaborations. It's a collaboration which has been ongoing with Ciba-Geigy. It started off as a contractual agreement. We would provide them with IGF-1; they would do all of the development. In essentially giving up all of our interest in subsequent development of the drug, we gave up a lot of our leverage if they weren't being aggressive enough in developing it. It's one of Bill's pet peeves over the years. I think that may finally be changing. We've finally nine years later restructured the agreement because we haven't felt that they've been as aggressive as they might be. Genentech is developing IGF-1 quite aggressively. It fits in very much with human growth hormone, which is their biggest product now. A lot of the effects of human growth hormone are mediated through IGF-1.

Bill's interest early on was the diabetes angle because IGF-1 can be insulin-mimetic. There are cases when people have insulin-resistant diabetes where you give them more insulin and it doesn't do any good. IGF-1 may in some cases be able to bypass that problem and cause them to respond better. It's like a lot of recombinant proteins, especially in the growth factor area: They're molecules in search of indications. They're well tolerated. There are few side effects. In high doses there are some side effects with IGF-1.

Chiron's AIDS Vaccine Program

Dino Dina and Jay Levy

Rosenberg: On to HIV. Dino came to Chiron in probably '82 or '83.

Hughes: Eighty-two.

Rosenberg: Early on Dino had gotten interested in HIV. It wasn't called HIV then. As I told you, he had been at Albert Einstein in New York where a lot of the original cases were described. Dino pushed pretty hard early on that we ought to be working in this area. No one could figure out, was it a virus, wasn't it? In the early days no one really knew whether it was going to be a big health problem or not. We were on to it very early on before a lot of people had thought about it.

Hughes: Dino didn't start on it in 1982, did he?

Rosenberg: I don't remember. We probably cloned the virus in '84? [checks chronology] First cloning September 1984. We talked about it probably in early '83. Shortly after Dino came, we talked about it as a potential project. "We" being Chiron as a whole. It just hadn't become clear that it was an infectious agent, that it was going to be a health problem. Was it worth working on? It wasn't obvious. It seems crazy in retrospect. And we finally got into it.

Dino to his credit really thought it was something worth doing and subsequently started a collaboration with Jay Levy, who is at UCSF. Jay is a virologist but not a molecular biologist by training. At least he wasn't then. Jay was interested in a collaboration that could develop his virus. There was so much politics and competition at that point about whose virus it was. Was it [Robert] Gallo's virus? Was it [Luc] Montagnier's virus? And Jay had a completely independent isolate, which turned out in the long run to be very important for us. Scientifically and politically and financially it was important for us to have a completely independent isolate.

Working with a Lethal Virus

Rosenberg: Fairly early on no one knew anything about this virus. It wasn't clear this was really the agent that was important in AIDS. We were pretty convinced at that point it probably was. And then the question was, okay, what sort of containment to use.

Hughes: Was this the first really infectious agent that Chiron had worked with? Oh, you had worked on hepatitis B.

Rosenberg: Hepatitis B is much more transmissible than HIV, and we hadn't started working on HCV yet, at least not in a major way.

Hughes: Chiron had the control systems in place because of the hepatitis B work?

Rosenberg: Yes. I can't remember when I was put on the biosafety committee. It was pretty early on. We thought real hard about this because there was a lot of concern among the people who worked at Chiron. People were pregnant; others were just scared. We didn't know enough about the virus and how it was transmitted at that point to know what sorts of levels of precautions were required.

NIH and the CDC had put out guidelines. Even though they said, as I recall, that one should use BL [biosafety level]-2 containment for HIV, we decided in the biosafety committee, for scientific and personnel and political reasons that we were going to do everything BL-3 with HIV. Chiron built a special BL-3 facility to deal with that in the virology group, because we weren't sure everyone knew enough about the virus and how it could be transmitted.

We had a lot of people who were very concerned about it in house, even people with a fair amount of expertise in virology. And we were sure that the community would be very upset if we ever had any problems with it, so we wanted to make extra sure that we were going even further than was actually required by law.

Hughes: Is BL-4 the top?

Rosenberg: Yes. And if you're interested, there's a fantastic article in the latest *New Yorker* on dealing with BL-4 viruses.

Retrovirology

Hughes: That would be interesting.

Rosenberg: It's scary as hell. [laughter] It makes AIDS seem like an easy virus to deal with.

We finally made the decision that we were going to start working on AIDS vaccines. Paul Luciw had come from [Harold] Varmus's or [J. Michael] Bishop's lab at UCSF. He's also a virologist. Dino, Paul, and Steve Potter, who was a technician working with Dino at the time, were the people who were involved in doing this. Dino had had a lot of experience with retroviruses up to that point. That had been his training and his own research. He was a postdoc with Peter Duesberg of HIV fame. He and Peter had a falling out, and Peter kicked him out of his lab. Peter's a little nuts. Dino then spent the last year of his fellowship working with Ed Penhoet at Berkeley, also with support from Mike Chamberlin, who I postdoc-ed with, which is how I got to meet Dino early on. That was in the mid-seventies, late seventies.

Retrovirology was one of the most interesting areas in virology because these are transforming viruses, except for HIV which is not a transforming virus. The reason people study retroviruses is because they have oncogenes in them. They are viruses that have picked up oncogenes. In fact the way a lot of these original cellular oncogenes were identified was because they were viral homologs.

Hughes: Why would retroviruses pick up oncogenes as opposed to other genes?

Rosenberg: Well, it gave them a selective advantage because they would immortalize the cell that they would replicate in so they could make more virus. That's the short answer.

Hughes: That's good enough.

Rosenberg: People were interested in transforming retroviruses because this was a way of studying cancer where you knew what the agent was that transformed the cell. Almost all the oncogenes, at least those that were initially discovered, were discovered because there was a viral homologue that a transforming virus had picked up. You could show that's what made it transforming. Then people found that in a normal cell the same molecule or a closely related one existed. They said, "Aha! This must mean if this molecule is misbehaving in some way, it can cause transformation." In fact, Mike Bishop and Harold Varmus got the Nobel Prize for hypotheses along those lines.

To get back to HIV: I think Dino and company went over to UCSF and got this virus. There were a lot of negotiations about royalties and this and that--if anything ever came of this research what would happen. I'm sure Dino can tell you stories about that with Jay.

Research by the Chiron Team

Rosenberg: A lot of the work in handling the virus was initially done at UCSF until we had our BL-3 facility built. We didn't want to have the virus over here before then. We finally got that taken care of and a number of people were involved in isolating enough virus to then make DNA and to clone. It took a while and we weren't as successful as we initially thought. There was a lot of, "It's trivial! Why haven't we done this already?"

Steve Potter who was working with Dino at the time--he's now in project management here--made the library where he cloned the virus. But you couldn't clone the whole virus. The NIH regulations said you couldn’t clone more than half of the virus. So we had to make sure that we used a cloning strategy that would give the virus in pieces, which makes it harder to put it back together to know what's going on. Because of biosafety, we didn't want to have a pro-virus intact because then we should probably be using BL-3, and it's very difficult to work under BL-3 conditions. You gown up. You have lower air pressure inside the lab than you do outside, so if anything breaks air comes in; it doesn't go out. It's not quite like a space station--that's BL-4. So by only cloning halves, we could do that in BL-2 conditions. The biosafety committee felt comfortable about that.

So they got the clones, and then a number of people, Ray Sanchez-Pescador and Rick Najarian--I don't remember who else--three, four, five people worked around the clock and sequenced the whole virus in a week.

Hughes: Ahead of everybody else?

Rosenberg: Well, we, Gallo's group, and Montagnier's group all published papers on the sequences within a month of each other. They had obviously been working on the virus a lot longer than we had.

Chiron's First Press Conference

Rosenberg: After that was done, we called the first press conference to announce that we had isolated the sequence of the virus. We had never called a press conference before, and we didn't have any idea what to expect. And there was press everywhere! We didn't know what we were doing. It was really funny in retrospect.

Hughes: Did Chiron have a communications office?

Rosenberg: I don't know if we had a PR person at that point. I think we did. From that point dated our abysmal coverage in the *San Francisco Chronicle*. Whoever the science person was at the *Chronicle* wanted an exclusive. He wanted to know before anybody else what we were going to talk about. We wouldn't give him an exclusive and he got pissed off. We've hardly gotten any coverage in the *Chronicle* ever since--still! It's still true.

Hughes: Was that Charles Petit?

Rosenberg: I think so.

Hughes: What happened at the conference?

Rosenberg: I just remember chaos. The press trying to get in the back door. We didn't have it well organized. So that was the beginning of the HIV story.

HIV Diagnostics

Rosenberg: And then we screwed around for a long time. We were really ignorant about what it took to make diagnostics work. We could easily have had the first diagnostic product on HIV in a year if we'd had any idea what we were doing. But we didn't.

Hughes: Did anybody?

Rosenberg: Well, what people used initially were viral isolates. But we wanted to do it by recombinant DNA. The problem was we thought we knew what were the important regions for diagnostics based on other viruses. But it turns out that there were some funny things about HIV, so regions that you wouldn't at all expect to be important in being antigenic in people <u>are</u>. Instead of taking a strategy where you would express lots and lots of pieces of the virus and then look at people who were seropositive who had HIV and ask which parts were the ones that correlated with these sera, we said, "Okay,

it's got to be envelope, and it's got to be this, and it's got to be that." We were wrong. We missed one of the key epitopes. We spent years trying to develop HIV diagnostics.

An Independent Viral Isolate and Patent Position

Rosenberg: Just this week we issued a very important patent on HIV diagnostics. We have a patent on any diagnostic which uses part of the envelope chain in recombinant DNA. That will cover all the diagnostic tests for now. So we will subsequently get royalties on that even though we didn't know how to make them ourselves. It's only years later that we learned how to do this properly.

There were a couple of things that were key in terms of doing it the way we did it. The isolate that we worked with was called SF3--I think that's right. San Francisco isolate 3, which came from Jay Levy's lab. It had some other names too.

Hughes: That's the one that's still used in the vaccines?

Rosenberg: Yes, exactly. Well, it turns out that is a field isolate. It was isolated in San Francisco and is very different from the isolate that Gallo and Montagnier characterized initially. This turns out to be much more typical in its sequence with a lot of other field isolates, and probably is a better immunogen and will cover more of the isolates that are clinically relevant than HTLV-IIIB, though that's still a matter of some conjecture. Because we had a completely independent isolate, we were outside all the Gallo patents and all the fights about it. We took an independent course. The government licensed a number of groups to try and develop diagnostics. As I recall, we didn't get chosen as one of the groups to do that. But we had an independent pathway because we had an isolate and our own patent position. So that turned out to be very important.

Hughes: More recently the state of California has given Chiron considerable money to develop a vaccine.

Rosenberg: Yes.

Kathy Steimer, who has been at Chiron for a long time, eight or nine years I think, is the head of the project now. Nancy Higwood was co-project leader with Kathy until last year. She left about six months ago to go to Bristol-Myers in Seattle. They and earlier on Paul Luciw, who was involved in the project, had done a really excellent job in developing that project.

Advantages of the Chiron Vaccine

Rosenberg: The key thing turns out to be that because we were working on several vaccines, we developed some core technology in the adjuvant arena. That may be our key advantage in the vaccine area. We've got an adjuvant which will be approved for use in people

that is really superior to what anyone else has. I think it will be useful in HIV and it also is clearly useful in herpes vaccine trials.

Hughes: So it's more the adjuvant than the antigen which gives the Chiron vaccines an edge?

Rosenberg: It's both. It turns out that learning how to make gp120, the envelope glycoprotein of HIV, in a form that's native is tricky. It's not an easy protein to work with. It's very touchy. And so figuring out that was key and figuring out a process for making it was very important. Some of Genentech's initial experiments didn't work very well because they, and at the time probably we, didn't appreciate some of the subtleties in the molecule.

Hughes: They're working with a different molecule now, gp160?

Rosenberg: No, they're still working with gp120. There's actually another controversy now about gp160.

The MicroGeneSys Vaccine

Rosenberg: There's a small company in Connecticut called MicroGeneSys that works with that, and they just managed to get a $20 million slush fund in the defense budget approved through the back door to try and put that into vaccine trials ahead of everything else. It has caused a big scandal about who ought to be regulated, how, and which molecules go into trials. [NIH Director] Bernadine Healey rightfully says it ought to be the NIH and the scientific community that say these are the vaccines we want to try, and not whoever can get a lobbyist to give them $20 million dollars to put into the defense budget. This is crazy.

Hughes: There is also the issue of putting all your eggs in one basket by sponsoring only one vaccine.

Rosenberg: Well, yes. It doesn't make sense.

Hughes: Of course there are issues connected with the clinical trials of any vaccine, but particularly of one for HIV.

End Points for Vaccine Trials

Rosenberg: It's difficult to know how to structure an HIV clinical trial. Do you define the end point as efficacy? Since we know how the disease is transmitted, you can pretty much rule out getting AIDS.

[Tape 3, Side B]

Rosenberg: A problem with designing clinical trials is that since you have a good idea how to prevent transmission, and you want to vaccinate people, do you vaccinate them and then give them a license not to practice transmission prevention to see if your vaccine works? That doesn't seem like the right thing to do.

The difficulty is, you will never be able to demonstrate efficacy because you will never get enough people who will be exposed versus a control population which isn't vaccinated. So people have talked about using surrogate end points. If you can demonstrate that people develop high-titer neutralizing antibodies that will neutralize a relatively wide variety of viral isolates in culture and it's safe, is that good enough? Well, you haven't proven that you're preventing transmission the way it happens in people, with complications between how the virus really replicates and how it's transmitted. Is it transmitted as free virus or as virus in infected cells? It's a complex problem.

The alternative appears to be that you want a trial in Africa or somewhere else in the third world where the disease appears to be transmitted differently, in the sense it appears to happen much more in heterosexual sex than homosexual, and where perhaps the educational problem is more difficult because there are more cultural barriers to getting people to change their behavior. But there are real ethical issues there as well. Wouldn't you rather take the money you're spending on the vaccine and try and educate people instead? It's got to be cheaper in the long run. So I don't know how that whole situation is going to sort out.

My understanding is that in the next year NIAID, National Institute of Allergy and Infectious Diseases, will sponsor a number of vaccine candidates in fairly large-scale phase III trials in this country. I can only guess that they will be done with surrogate end points because otherwise, even with the government being willing to pay for it, you're never going to be able to demonstrate efficacy. And so you have to say, "Okay. It's safe, and it appears to give the right characteristics. We're just going to approve these things in people and see what happens." It's not exactly a situation you want to be in, and I think it's very complicated.

Hughes: Isn’t there a need to loosen standards because AIDS is a fatal disease?

Rosenberg: Sure. It's certainly true in the treatment modality, and one wants to relax the standards, yet at the same time try and protect people from charlatans.

Trials in Chimps

Rosenberg: The requirements for exhaustive pre-clinical trials before you try something in people-- If you've got a disease which you can only see in people and in chimpanzees, it's probably morally wrong to do testing in chimpanzees. Chimpanzees are an endangered species; humans aren't. People think I'm crazy when I say this, but I really think that you ought to treat people who have the disease as opposed to giving chimpanzees the

disease and then treating them. You need to demonstrate some level of safety; you don't want to kill people. On the other hand, as you said, if people have a fatal disease, what have they got to lose? Why are you endangering chimps, which aren't that good a model in HIV anyway. That's another whole topic.

Other Issues in Vaccine Trials

Hughes: There is another issue: If you are going to test in the third world, are you then going to be able to price the vaccine at a level that the third world can manage?

Rosenberg: Well, I think the notion is that there is going to have to be some sort of alternate funding. The vaccine's going to have to be provided essentially for free to the third world. The same thing's true with malaria. The only market that makes sense for the malaria vaccine is travelers from the developed world who go to--pick your endemic malarial country--and they want to be protected, and they will pay a hundred bucks so they don't get malaria, or whatever.

To make the point even stronger, from the point of view of the economics of drug discovery and development, you can make a better argument for developing veterinary vaccines for the developed world than you can for human vaccines for the third world. That's crazy, but true.

I think it will have to be done through WHO and the United Nations. A consortium of the developed countries will have to say, this vaccine will be provided. And they will pay for it and then reimburse whoever did the development at some reasonable level. Whoever does come up with a safe and efficacious HIV vaccine will make plenty of money, even without the third world as a market. Forget about that; it's not an issue. You can worry about black markets: It gets shipped to the third world, then it gets black marketed back into the developed world.

Advantages of the Chiron Vaccine

Hughes: Is it the adjuvant that gives Chiron the edge in the race for the vaccine?

Rosenberg: It's probably a combination of two things I mentioned before. The adjuvant clearly is key. We set up a deal with Ciba-Geigy because they had what we thought was an interesting adjuvant, and we have the antigens.

Hughes: For HIV, or for a lot of vaccines?

Rosenberg: For all vaccines. Work that was subsequently done at Chiron is in large part responsible for the advances in the adjuvant technology and less so the initial work that attracted us to Ciba-Geigy in the beginning. It turns out to be sort of black magic. It's a formulations issue more than anything else. How do you formulate something so that

it's a good immunogen? It depends on how you make the antigen with the adjuvant in particles. And the questions are, what is the optimal size of the particles and what is the ratio of adjuvant to protein? You need to be very careful in how you manufacture the protein because it has got to be a native structure. Those two things together are the key. Other people, including Genentech, have figured out how to make the native form of gp120. But I think we have a better position in the adjuvant side of things.

Biocine and Sclavo

Hughes: Does that change the partnership with Ciba-Geigy?

Rosenberg: The Biocene company--and Dino can certainly speak to this in more detail--has become very much an independent company. It's got an independent chief executive officer now, Jacques Martin who is based in Lyon, and with the purchase of Sclavo probably all of the pre-clinical and clinical work is being done either in Emeryville or at Sclavo. There isn't any real in-house effort at Ciba-Geigy. What Ciba-Geigy has provided is funding and will certainly provide a sales force. That may even be done independently. And they've spent a lot of time and effort developing a business plan for the Biocine company.

Hughes: Why was Biocine set up relatively independently?

Rosenberg: I think it evolved that way.

Hughes: Does that present problems?

Rosenberg: Oh, I think it has probably been the source of some tensions here and there. Chiron has a tendency to be a birthplace of companies or businesses that get spun off like tornadoes off of a hurricane. A lot of the initial research was done at Chiron, and then we needed to get business and financial and some scientific input from Ciba-Geigy.

Then we decided, to make this a real business that works, you need to get input from the pediatric vaccine area, so you buy Sclavo. The key point later on in development is the fact that we will have a proprietary position in hepatitis C vaccine development, which is going to be what will give us leverage with the major vaccine companies. There are really only three vaccine companies in the world--Merck and SmithKline and Merieux. But Merieux works with one or the other; I can't remember which.

Chiron's at an interesting stage in its development because we're partway between being a single company and developing into separate companies. And there are still a lot of connections but they're becoming less and less strong as a function of time as the various businesses, business units, I guess they call them, develop more and more identities, and their needs become differentiated from other parts of the company.

Business Units and Other Models for Expansion in Biotechnology

Hughes: What does that mean for Chiron itself?

Rosenberg: Well, I think you can see Chiron in another decade or so evolving into more of a holding company, with perhaps central corporate activities being associated with it--maybe research. But research might eventually evolve into being vaccine-specific or therapeutic-specific or diagnostics-specific. There's already some of that going on. It has all been in a common technology base, certainly for the first decade of the company's existence. But all those things change, and we're developing new technologies and taking advantage of them, and there are different emphases in different parts of the organization. One could argue that Chiron should be more aggressive in letting these companies develop independently.

Hughes: What would the argument be from Chiron's standpoint?

Rosenberg: The argument would be that if you made it as an independent company you can get additional financing from the outside. It would be less constrained by Chiron's overall promises to the financial community about how they would perform. For example, we've got an extremely profitable diagnostics business right now, which just doesn't look profitable because it's supporting everybody else. So you can say, well, Chiron ought to sell the diagnostics business. We could get a billion dollars for it, whatever, and use that money for something else. The diagnostics business ought to be a publicly traded company existing on its own. You can probably say the same thing about Biocine, though it's not profitable yet. I would not be surprised if eventually Chiron evolved into a holding company where there are a half-a-dozen or a dozen business which all were spawned out of the mother company.

Hughes: Is there any model for that in biomedicine?

Rosenberg: No, and certainly not in biotechnology. Johnson & Johnson is sort of that way, but I don't think it evolved from a central core; I think it was done by acquisition. But I don't know enough about the history of J & J.

Hughes: Amgen or Biogen or any of the older biotech companies haven’t done anything like this.

Rosenberg: Well, Chiron is by far the most diversified of the companies in the sense of being in lots of different businesses. Genentech has done it in a different way, which is that a lot of people who used to be at Genentech have started lots of small companies. But Genentech doesn't have any stake in those companies. Chiron has managed to hold on to those people by giving them enough independence--sometimes it doesn't seem like enough independence in a lot of people's minds--but at least enough so that they haven't gone off and done something else.

There's tension between two sort of models: having separate business units under the separate companies that are massed around a central infrastructure or central core versus really keeping the company under one roof. It's like centrifugal force. These things will spin off on their own momentum after time, because they get big enough and

they develop enough. They become very much differentiated. Chiron Ophthalmics is the best example; it's a separate business. I think these other businesses will become separate as a function of time, because as things get more mature, they become more customer-driven, perhaps to some extent less research-driven. The research becomes more focused in particular areas to complement pre-existing products that are on the market or whatever. Then it becomes a very different game, and it's interesting to ask: Can you maintain the same entrepreneurial flavor in that sort of environment? And we'll see.

Intellectual Property

Hughes: What efforts are made to safeguard intellectual capital, and when a person leaves, what kinds of restraints, if any, are put on them?

Rosenberg: Well, that's an interesting question. Ed Penhoet says that in the state of California you really can't constrain someone from practicing their profession--

Hughes: Why do you mention California?

Rosenberg: I think there may be some court rulings with regards to that, probably coming out of Silicon Valley originally.

Hughes: That seems reasonable.

Rosenberg: People have to sign a piece of paper saying, you will not work on projects that you worked on here for some period of time-- a year or two years. But realistically you can't restrain what somebody knows. The only way you manage to keep intellectual capital is by making the company an environment in which people want to work so they don't leave.

On the other hand, people do leave; they help start new companies. Eventually that will be beneficial to the industry and probably Chiron in particular because they'll come back and may be partners. They're small, and we're larger and help fund their efforts. So it's an evolution. Chiron in the last year or two has gotten to the position where it is asked almost as much to fund other people, as we ask people to fund us.

Onyx

Rosenberg: Maybe I'll talk a little bit about Onyx, because that's in that mode. Frank McCormick, who is the head of research at Onyx, had developed a research program at Cetus focused on oncogene signal transduction--how cells get transformed--and learned some of the details of the signaling pathways that are involved in transformed cells--how they differ from normal cells. It's a very hot area. Several new companies have been formed in the last year or so along those lines. It became quite clear that that group couldn't be

supported within Chiron at the level Frank wanted because as usual lots of other things are also interesting.

So the only way it appeared to make sense, and this may be a good model for the way some future developments will occur, is to spin off Onyx as a separate company, owned partially but not controlled by Chiron and partially funded by venture capital and also by the employees who own equity positions in the company as an independent entity. Onyx has loose ties to Chiron in particular areas, but sufficiently loose so they can get other partners, and then it can really function independently. We'll see how that works over the next few years.

But it gets a little complicated in the sense of cancer, because they represent at least one major area in which people are trying to develop anticancer drugs, and I'm not sure what the arrangement is at this point. If they develop things in that arena, does Chiron have first rights of refusal? We'll certainly know about it because we have one representative on their board of directors.

What you don't want to do is to set up a situation like that where you have competition. So we sort of divided up the cancer field to say, roughly speaking, that Chiron will work on molecules that work outside the cell, on the cell surface. And molecules that work inside the cell, Onyx will work on. I don't know what we'll do with things that stay in the membrane. We'll worry about those later.

It's very much an exploratory research effort at this point in terms of Onyx getting molecules which produce products. One of the reasons why it made sense to spin off the group was that it was clear for five years they weren't going to be having any products. And they were going to have a substantial deficit at a time when Chiron has some pretty ambitious financial goals. We didn't want to have all of the risk in that promising but long-term area; we wanted to spread the risk around. It's sort of a partnering deal in a different sense. It's an interesting model.

Hughes: Is a factor in all these decisions how Chiron is going to look in terms of the investment community?

Rosenberg: Sure. That's certainly a factor. I don't think it's an overriding factor, but it's a factor. We probably haven't been as creative as we could be in how we finance things. Chiron has always been pretty financially conservative.

Hughes: Is that due to the nature of the decision-makers?

Rosenberg: I don't know.

Hughes: Or does it have something to do with the fact that they aren't businessmen?

Rosenberg: It might. I think as a company we may be less comfortable with complex financial schemes for essentially laundering research funding, which is what a lot of people do. It's a way of getting the stuff off your balance sheet so the balance sheet looks better. You're still spending the money, and you're getting the money at very high rates of interest. It's complicated. I don't know what the right answer is in that regard. But it represents another way of leveraging your investments by only having part interest in

the company. Obviously you have less potential upside, but you also have less downside. It also enables you to give entrepreneurial people more visible positions, more responsibility, and more risk-taking on their own, so they can either succeed or fall flat on their faces. It's up to them.

That becomes an issue as a company gets older and as you get people who don't want to listen to someone else telling them what to do. You'd like to be able to provide room for them to keep within the Chiron family but to have enough independence so that they can do that and be satisfied with doing that–-a tricky balance to make.

Hughes: Well, Steve, you've been wonderful to give me all this time. Is there anything you want to say without prompting from me?

Rosenberg: Well, I hope to see this in writing some day.

TAPE GUIDE

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Current Position – 2003 to the present

Chief Scientific Officer, Expression Diagnostics, Inc.
XDx is focused on applying genomic technologies to immune mediated disorders

Recent Activities 2002-2005

Helped to grow XDx from 12 to 65 employees, to recruit a full-time CEO, and to secure financing of $30M. Led team which developed Allomap gene expression testing for detection of rejection in heart transplant recipients, launched in January, 2005.

Independent Consultant, Drug Discovery Technologies, Oncology, and Infectious Disease

Visiting Scholar, Department of Chemistry, University of California, Berkeley 2001-2002.
Designed and taught course on Drug Discovery

Other Current Activities

Member, Scientific Advisory Board Wilex AG
Member, Board of Directors, KMT Hepatech
Consultant: Chiron, Gilead.

Prior Activities

Issue Editor, Current Pharmaceutical Design, The Urokinase-type Plasminogen Activator System in Cancer, 2003.
Project Leader, Chiron-Pharmacia Joint Program on Hepatitis C Antivirals (1998-2001)
Project Leader, Chiron Urokinase Receptor Antagonists Program, 1995 to 2001

Head, Research Committee, Chiron-Amrad HCV Natural Products Collaboration (1996-1998)
Co-Editor, with Kasumi Shiosaki of Millenium, of Investigational New Drugs for Infectious Diseases, non-HIV Antivirals (1999-2000)
Member, Steering Committee, Chiron-Novartis Combinatorial Chemistry Collaboration (1995-2000)
Member, Research Committee, Chiron-Organon Drug Discovery Collaboration (1996-1999)
Trainer and member of the Executive Committee, UC. Davis Graduate Program in Biotechnology, 1992 to 2001.
Prior responsibilities in collaborations with Merck, Novo-Nordisk, Fina, Parke-Davis, Syntex, and Janssen.
Member and Vice-President, Board of Directors, Berkeley Biotech Education Inc., 1999 to the present

Education

Undergraduate:Brandeis University, Bachelor of Arts in Chemistry, 1973.

Graduate:Department of Biochemistry, University of California Berkeley, Ph.D. in Biochemistry, 1978: Thesis Advisor Dr. Jack F. Kirsch

Postdoctoral:Department of Biochemistry, University of California Berkeley in the laboratory of Dr. Michael J. Chamberlin July, 1978 to July, 1981

Membership in Professional Societies

American Association for the Advancement of Science

American Chemical Society

International Society for Fibrinolysis and Proteolysis

Previous Positions Held

Chiron Fellow and Senior Director, 1998 – May, 2001.
One of 3 Chiron Research Fellows.
Director of Biological, Computational and Structural Chemistry Departments
Extensive activities in research collaboration due diligence, management, and business development
Focus on oncology and infectious diseases
Additional roles as member of both Biological and Chemical Patent Committees, Target Evaluation Committee, and 401K Committee.

Senior Director, Chiron Technologies, 1995 - 1998.

Senior Scientist and Director of Biological Chemistry, Chiron Corporation, 1992 – 1995.

Senior Scientist and Acting Research Director, Protos Corporation, 4/89 to 1/92

Directed a multidisciplinary group that grew from 7 to 25 in the field of molecular diversity. The group included molecular biologists, receptor biochemists, peptide/protein chemists, and computational/biophysical chemists, and became the Chiron small molecule drug discovery effort.

Senior Scientist, Chiron Corporation, 10/86 - 4/89

Principal Scientist, Chiron Corporation, 12/83-9/86

Scientist, Chiron Corporation, Emerville, CA 8/81-11/83 - One of the original group of scientists at Chiron -Employee #13.

Research Assistant in the Department of Biochemistry, Brandeis University, in the laboratory of Dr. William P. Jencks: 6/72 - 9/72; 1/73 - 8/73.

Research Interests

Innovative methods for novel target discovery and validation

Novel targets and drug discovery in oncology and infectious diseases

Role of cell surface proteases in biology

Structure-function relationships in protein: ligand interactions as probed by site-directed mutagenesis, biophysical, and phage display methods.

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