Oral History Center
The Bancroft Library

University of California
Berkeley, California

William J. Rutter
Co-Founder and Chairman, Chiron Corporation

Interviews conducted by
Sally Smith Hughes
in 2004 and 2005

Since 1954 the Oral History Center of the Bancroft Library, formerly 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 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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William J. Rutter

This series of interviews documents **William J. Rutter's** view of his years, 1981-1999, as co-founder and chairman of Chiron Corporation, a San Francisco Bay Area biotechnology company specializing in vaccines and blood-screening technologies. These interviews explore the theme of commercializing basic science, introduced by the earlier oral history with Dr. Rutter on his career at the University of California, San Francisco. That interview can be viewed here: http://content.cdlib.org/ark:/13030/kt7q2nb2hm/

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Interview History by Edward E. Penhoet and Pablo D. T. Valenzuela

What you are about to read is a personal history of the founding, growth and ultimate success of Chiron, one of the small groups of companies which pioneered the biotechnology industry. We are fortunate to have this oral history by one of the most important figures in the history of the field. It is Bill Rutter's story but it is also our story, the story of all of us who helped him build Chiron and by so doing helped build an entire industry which has grown to thousands of companies with enormous impacts on business and medicine.

To all who joined Bill Rutter in the effort, Bill was an inspiration, a mentor, a partner, a consummate recruiter, a friend, an ever-present colleague, a fount of knowledge scientific and general, a seemingly tireless worker, a man who led by example, a brilliant negotiator, and, perhaps most striking, an individual deeply committed in every way to success for the organization. Finally, in the pursuit of any worthwhile goal, Bill was not always successful but never, ever, gave up. This list may seem far-fetched to many, but having observed Bill in action and having worked with him on a daily basis for almost twenty years, we can assure you that it is all true.

Chiron started as a trio but grew to an orchestra of thousands. The two of us were fortunate to be members of the trio and to work with Bill to build the enterprise from its humble beginnings in the abandoned labs of the Shell Development Company in Emeryville, CA. As indicated in the history which follows, we divided up the work and responsibilities among ourselves. Bill the chairman, Ed Penhoet the businessman, and Pablo Valenzuela the research director. We never had any illusions about who the senior member of the trio was, but we also enjoyed a working relationship with Bill that was based on mutual respect and collaboration, which we deeply appreciated then and still do thirty five years later.

How did these qualities of Bill Rutter influence the development of Chiron? Let us list the ways.

Inspiration: Bill always had lofty goals and generated enthusiasm in all those around him to stretch to achieve those goals. The goals were sometimes more than lofty, even seen by some as outrageous, but always serious: invent a hepatitis B vaccine, discover hepatitis C, make human insulin to treat diabetics around the world, sequence the genome of HIV, quantitate minute amounts of virus in infected patients, etc. These goals were embraced by Chiron colleagues and led them to work extraordinarily hard to achieve them. Many of them (including us) did their best work as scientists under Bill's leadership

Mentorship: Throughout Bill's career, he has made himself available to anyone with a serious interest in science and/or its application to health. At Chiron, Bill was available almost literally 24/7. Colleagues found him approachable, an engaged listener, and active advisor. His enthusiasm was infectious and his encyclopedic knowledge of the fields of biochemistry and molecular biology was readily shared.

Partnership: Although he always had a point of view and was clearly the senior executive at Chiron, Bill always treated us and other senior members of our team as partners, taking the time to hear our points of view and discussing issues thoroughly before coming to conclusions—

which to be fair were most often what he wanted to do in the first place but achieved without "pulling rank".

The consummate recruiter: This skill of Bill's has been a major factor in his success at both UCSF and at Chiron. These abilities were one of the keys to Chiron's success. His first major recruiting effort in building Chiron was to recruit us. One of us (EP) was a tenured professor at UC Berkeley and the other (PV) had a very attractive offer from a competitor biotech company. Nevertheless, we both took the risk to join a company which at that point existed only in the mind of Bill. This was followed by the recruitment of many people to Chiron, and Bill always played a key role in the effort. The results of this effort were clearly demonstrated by the success of the company and by the fact that many Chiron alumni went on to be leaders throughout the biotech industry—CEOs, COOs, CSOs, CMOs all grew up in the Chiron organization

Friendship: A person who gives assistance, a supporter. Bill has always been extremely loyal to his colleagues and has supported and helped all those close to him, including us among others. People throughout Chiron never had any doubt that Bill was there to help and support in many ways.

Ever present and tireless worker who led by example: Bill's work ethic is legendary. It is no exaggeration to say that he has worked harder in his career than most people can imagine themselves doing. This work ethic is infectious and his leadership by example has manifested itself both at UCSF and Chiron. In both environments, there was literally never a time when a visitor could not find someone at work at 3AM, on Sundays, on holidays. People did this because they were motivated to succeed and knew that the chairman was likely to be at work himself whenever they were.

Brilliant negotiator: One of us (EP) was deeply engaged in almost all the major transactions of the company and can say that he was often amazed at some of the negotiating positions Bill took. Much to many people's surprise, however, Bill frequently got what he wanted or something close to it, sometimes by the force of his arguments and perhaps often by simply wearing down the other side!

Commitment: When Bill decides to do something, he is "all in", as they say, and he never gives up on his goals. In the case of Chiron it was clear from the beginning that he would do whatever it took on his part to be successful, and this commitment was evident and animating to all those around him. Do that extra experiment, write that paper today, file that patent application this afternoon, and on and on—the things that come with commitment that people in nine-to-five jobs would never understand.

Hopefully this short introduction gives you, the reader, an insight into the life of the remarkable man whose history is recorded here and allows you to understand the influence he had on the company. Chiron was an amazing experience for all of us on the inside and a huge contributor to human health around the world. It is no exaggeration to say that millions of lives have been saved by the work Chiron did and also to say that none of this would have happened without the visionary and determined leadership of William J. Rutter

William J. Rutter Interview History

William J. Rutter, co-founder and chairman of Chiron Corporation, an early biotechnology company formerly located in Emeryville in the San Francisco Bay Area, provides a first-hand account of the complexities of founding, funding, and administering an entrepreneurial company based on new genetic and biochemical technologies. A major theme is the accelerating commercialization of bioscience beginning in the mid- to late 1970s. An earlier oral history on Rutter's years (1968-1982) as chairman of the University of California, San Francisco Department of Biochemistry introduced this theme and the resulting tensions that the first steps in industrializing the basic science of molecular biology provoked within academia.

http://content.cdlib.org/ark:/13030/kt7q2nb2hm/

Entrepreneurial at heart, Rutter predictably could not sit idly by as he watched colleagues forming companies grounded in the new technological breakthroughs and graduate students and postdocs leaving universities to join the new startups.

The present oral history, continuing the commercial theme, begins with Rutter's account of his association with three pre-Chiron entities seeking to profit from the practical applications associated with genetic engineering. He gained further business experience on the scientific board of Amgen, a biotech firm founded in California in1980. From these experiences, he developed ideas about how small entrepreneurial firms might be organized and managed, whetting his desire to forming a company of his own. In the spring of 1981, Rutter invited Edward Penhoet and Pablo Valenzuela, former members of his UCSF lab, to discuss founding a startup. Captured by Rutter's vision, they sketched out a business plan centered on producing human insulin and a hepatitis B vaccine and including a projected effort in diagnostics.

It was a risky proposal. None of the three had formal business training or knew anything much about venture capital as a source of startup funds. Furthermore, vaccines in the aftermath of Cutter Laboratory's disastrous experience with a defective polio vaccine prompted the pharmaceutical industry to label vaccine manufacture as an area prone to liability issues. However, the threesome felt that the prospective company could circumvent the liability problem because their vaccine was built upon a noninfectious recombinant particle. With Rutter as chairman, Penhoet as CEO, and Valenzuela as director of research, and scientists recruited largely from Rutter's lab and the earlier companies, Chiron, as it came to be known, began operation in 1981. Bowing to academic unrest over his corporate interests, Rutter resigned as department chairman in 1982, becoming director of UCSF's Hormone Research Institute where, with less controversy, he continued to keep close tabs on the company. In 1989, he joined Chiron fulltime.

As a participant in virtually every major decision, he is in a prime position to describe key events in the ups and downs of Chiron's history. And downs there were in the fierce competition among biotech firms to patent, license, and capitalize on the potentially lucrative products of genetic engineering. Chiron did not always win out despite Rutter's strategic sense and innate competitiveness. But as the oral history documents, the highlights were memorable, among them, development of path-breaking blood-screening technology, establishing the importance of viral load in measuring the severity of infectious disease, and isolation of the hepatitis C virus. In

1991, Chiron bought Cetus Corporation, its next-door rival in biotechnology but could not afford to purchase its PCR technology which went instead to Hoffmann La Roche. Chiron itself was acquired by the Swiss pharmaceutical giant Novartis in 2006, seven years after Rutter had left the company. An era had ended. But Rutter went on to fund and advise a handful of small companies, an activity he continues at the age of 87 at the time of writing.

But what about the man himself? The following exchange reveals Rutter's management style and suggests his commanding personality:

> Hughes: …if you were asked to characterize your management style, what would you say?
>
> Rutter: Interactive, vigorous, and driving, forceful.
>
> Hughes: Authoritarian?
>
> Rutter: Perhaps a bit, in the end.
>
> Hughes: So you would consult, but then make the decision on your own?
>
> Rutter: Well, I honestly don't think that I dismissed other people's ideas, and frequently I enthusiastically accepted other people's ideas. But I took responsibility of making the decision in the end, taking into account, hopefully, all the various points of view. I was cognizant of the competition we were in, and I don't like to lose competitions. I don't think I was directive, but I like things to happen. Not always was it my decision, not always was it my idea going in, but when it came to making a go, no-go decision, yes, then I could make a decision. And that was my role.

The five interviews compiled herein were recorded between September 2004 and July 2005 in Chiron's Office of the Chairman of the Board. A man who keeps himself insanely busy, Rutter every now and then would re-visit the task of reviewing the transcripts. The process took ten years to complete. A stickler for precise English and clear prose, he edited heavily, often rephrasing as well as adding pertinent information. The result is something less than an exact transcription of the original interviews and something more in terms of its deeply informative content.

This oral history is one of six in the Bancroft's series on Chiron which features interviews with early administrators and scientists.

http://vm136.lib.berkeley.edu/BANC/ROHO/projects/biosci/oh_list.html

Those interested in the early history of commercial biotechnology may wish to consult the interviews on Genentech, Cetus, and Amgen, also available at the link above. The eclipse of Chiron, Cetus, and Genentech through acquisition by pharmaceutical corporations makes this and other oral histories in the biotech series all the more important as chronicles of their histories as independent entities.

The Center for Oral History is a division of the Bancroft Library and is under the direction of Neil Henry. Special thanks to Julie Allen for creating the table of contents and preparing the transcripts for online presentation.

Sally Smith Hughes
Historian of Science and Project Director

Berkeley, California
November 2015

William J. Rutter, Ph.D.

Corporate Activities:

Synergenics, LLC:	Chairman/CEO – 2002-
Chiron Corporation:	Co-founder of Chiron Corporation; Executive Chairman from its inception in 1981-1999; Chairman Emeritus, Chiron Board 1999-2003
Ventria:	Founding Chairman, Board member, since 1992. High level production of proteins in cereal grains, specialty: orally active human therapeutic proteins.
iMetrikus:	Chairman, Board of Directors, Founder, since 1999. Automated data capture from any electronic metric device to form an individual health record accessed via internet (computers or cell phone) by health care providers, or anonymously to other health care companies, and third party payers.
PraxSys Biosystems:	Boardmember 1999-2001. Chairman 2001. Rapid quantitative immuno analyzer for point of care diagnostics, worldwide markets.
Synco-BioPartners:	Founder, Chairman since 2000. Process Development and small scale manufacturing: Therapeutic proteins/vaccines in Amsterdam Netherlands.
Synergenics, LLC:	Founder, Chairman, CEO. Consortium of concept stage biotech startups; providing strategic scientific/business advice. Legal/financial services, and facilities. Companies: ReLia Diagnostics, Picobella, Poetic Genetics and Synamem, Inc..

Other Board Memberships

Sangamo BioSciences –1999 -
Cytokinetics – 1999 –
Poetic Genetics – 1999
NuGen Inc. – 2002 -
Oscient Pharmaceuticals – 1999 –
Epitomics – 2003 -

Academic Affiliations/Activities

Harvard College – B.A. 1949; University of Utah – MS 1950; University of Illinois, Ph.D. 1952
University of Illinois – Professor biochemistry 1955-1975
University of Washington - Professor Biochemistry/Genetics 1975-1979
University of California, San Francisco – Hertzstein Professor – Chair Biochemistry / Biophysics 1979-1982; UCSF Director, Hormone Research Institute 1983-1990

Publications

>380 Scientific articles
>20+ patents, patent applications

Other Activities

Harvard University Board of Overseers	1992 - 1999
Carnegie Institution of Washington	1995 - 2003
Board of Trustees	
Senior Trustee	2003 -
Bay Area Life Science Alliance,	1997-2002
U.C. Mission Bay Campus LLC, Chairman	

Professional Affiliations

National Academy of Science (NAS) 1984, Counsel 1984 - 2003
American Academy of Arts and Sciences 1987

Selected Awards

1995	Heinz Award for Technology and the Economy
1999	Jacob Heskel Gabbay Award in Biotechnology & Medicine
2000	The Bower Award for Business Leadership from the Franklin Institute
2003	The Chemical Heritage Foundation 2003 Biotechnology Heritage Award
2004	Bay Area Business Hall of Fame

Interview with William J. Rutter
Interviewer: Sally Smith Hughes

[Note: The narrator has substantially edited these transcripts. They do not closely match the original sound recordings.]

[Interview 1: September 11, 2004]

[Tape 1, Side A]

Hughes: Your UCSF story is pretty well covered in the first series of interviews, I feel.[1] So the point of this next series is to do a similarly comprehensive history of Chiron. But before we get to Chiron, I'd like to hear about your earlier commercially related ventures, setting aside the relationships you've had as a consultant, which we have discussed previously. Let's start with the California Institute for Genetics Research, which was founded in the late '70s.

Rutter: Yes. When it became obvious that there were many projects of commercial relevance, for both the technology and for the members of the Department of Biochemistry and Biophysics at UCSF, I sought general mechanisms to develop some kind of coherent approach to the use of the technology. One approach was to set up a development lab, a technology transfer lab, that was affiliated with the university. I patterned it conceptually with the labs that were set up at universities for the development of radar and other defense-related subjects in World War II. Those programs were extremely useful and efficient. They had the advantage, I thought, of developing a general approach, which would then build on the technology itself and provide many of the aspects (components) of the technology which were not available centrally for each of the programs at UCSF—like the synthesis of nucleic acids and so on. And it would keep the highly integrated scientific and cultural system that we developed at UCSF intact.

To that end, we explored the foundation of an institute which could operate side by side with the university, and in that way develop applications and technology that had started in Herb Boyer's laboratory, but also in other laboratories too, particularly Howard Goodman's, which was interested in nucleic acid synthesis and the fundamental technical approaches to cloning. That would fuse then with the more focused interests of not only mine but many other people in the faculty. So the California Institute for Genetics Research was a result of that line of thinking. It was an exploration with a distinguished attorney, and I took on this obligation by myself, paid for his services. We actually did set up the institute. On the other hand, the university saw no easy way to support the institute. It didn't have available space. It was

[1] The earlier interviews with Dr. Rutter are found at http://content.cdlib.org/ark:/13030/kt7q2nb2hm/

difficult to imagine that the institute would be incorporated directly in the space of the department. It wouldn't have been appropriate.

Hughes: Because it was a commercial entity?

Rutter: Well, it was a halfway house. It wasn't commercial per se. But we would have had to pay salaries competitive with commercial companies in order to retain the key personnel. They were discrepant to the university's salary.

Hughes: And how were departmental personnel expected to interact with the institute?

Rutter: Well, the general idea was, they could participate in any programs that were there. The institute itself would have central facilities, and we'd work on the development of a project up to the point where it could be transferred to an external commercial organization, presumably a pharmaceutical company, a chemical company, or whatever.

Hughes: And would the faculty receive an additional salary, or would this just be an enhancement of their own research agendas?

Rutter: They could receive additional salary, but salary was not a major issue, I didn't think at the time. Immediate remuneration of the faculty and staff was not an issue. But in the context of a contract and consulting in relationship to a contract, they would have had the ability to accept an additional stipend.

Hughes: The fact that the university might put a stamp of approval on this concept could avoid the turmoil that was surrounding Herb Boyer and others who had wholly commercial ventures as well as their academic positions?

Rutter: Well, in principle it would have because it would have put everybody in the same boat, and the technology transfer wasn't a commercial operation in itself, that is, a commercial enterprise by standard criteria. The California Institute for Genetics Research was established prior to the very vibrant and divisive controversy over commercialism in academic biology which occurred in the department and in the university at that time. But yes, I did believe it would have dissipated many of the concerns or antagonisms concerning this technology and its relevance to industry. The university, the dean and chancellor, supported the concept— that is, they were permissive. But I believe they only supported it halfheartedly. They could provide no resources, either in terms of facilities or financial resources to start the institute. It had to be self-funded totally. Given the other complexities that I mentioned—salaries—and the fact that we already had a key figure [Herbert W. Boyer] starting a company, the California Institute for Genetic Research was a non-starter. Frankly, looking at it thirty years later, it probably was not a good idea. It could not have been competitive and would have been competitive to the vibrant extrinsic support which was to fund the emerging biotech industry.

Hughes: Why do you say that?

Rutter: I say that because I believe that halfway houses never truly deal with the problem. The issues that are best handled in an academic environment should be developed within the academic environment. When it becomes commercial, and you have an explicit problem to solve, it's best to develop the resources and the team that's going to execute, and focus the team on more than just the short-term development. The ebullience of the whole biotechnology industry is a testament to that. I don't believe there's any university that has set up such a development lab, save in wartime for defense oriented projects. It was a dream I had because of my involvement and my commitment to the UCSF biochemistry department and the school of medicine.

Hughes: Was it also your feeling that much of this science and technology had been developed in academic labs but then was being skimmed off by the corporate world without adequate compensation to the universities?

Rutter: Well, I don't see it that way. I don't see the university as a profit-making organization. Universities' research programs were developed from funds supported largely by the U.S. government and other agencies. So the university does not "own" the technology by virtue of the investment of its own resources. Through the largesse of the government, via the Congress, the university was able eventually to gain the rights to the technology derived from research grants from the government (NIH, primarily). This represented decentralization of the management of the research enterprise and also an incentive to the universities to engage in practical research to the benefit of society—a remarkably farsighted and in hindsight, effective strategy for development of an industry based on discovery and technical innovation and support of science education.

Hughes: Through patenting, you mean?

Rutter: Through patenting, know-how, transfer—all of those things. That created a very great source of revenue for both individuals and for universities. However, in the grand scheme of things, the government's role is developing technology in order to produce businesses which in turn pay taxes and hire people and create a livelihood for people—that's the way our society works. I do not see that the university as an organization is treated unfairly. In fact, the university is treated immensely fairly, because the university doesn't have those resources to begin with; they are in this case provided by the government.

Hughes: Meaning the federal government or whatever.

Rutter: Mostly the federal government or foundations. So fundamentally, all that research is carried on on behalf of, largely, the taxpayer. And so creating an

industry and the wealth associated with the industry, creates a source of taxes and a source of employment which helps the entire population, hopefully decreasing in the end healthcare costs or increasing the quality of life.

Hughes: Therapeutic Biopolymers was how Chiron was originally incorporated.

Rutter: That's right.

Hughes: Well, tell me about Therapeutic Biopolymers.

Rutter: That company was originally championed by two of the more inventive and entrepreneurial postdocs, namely Mickey Urdea[2] and C.K. Chang, who was an unusual person. C.K. ran the stockroom at UCSF. He was a member of a Chinese trading family and with some [financial] resources. So the firm was catalyzed by both C.K. and Mickey. The aim was to provide nucleic acid polymers, which in their absence were a roadblock to doing genetic engineering.

[Tape 1 Side B]

Rutter: There were no companies that synthesized nucleic acids, and Mickey knew the technology well. We set up a small group to produce nucleic acids, not only for the lab and the university on a commercial basis, but also for others as well.

Hughes: Was this company using the method for synthesizing DNA that began with Gobind Khorana and then got modified as it was passed down through his students?

Rutter: Well, there were various methods of making nucleic acids, but Gobind was clearly a pioneer in that field, for sure, and there were better methodologies that were coming along, chemical methodologies. This was not a discovery-based technological company; it was a service company based on available, published for the most part, chemical methodologies. It was a situation where there was a specific need for the efficient production of nucleic acids. We couldn't do that within the university. So we made a proposal, and I agreed to support it, because I thought it was important, and I also particularly admired Mickey and C.K.'s entrepreneurial spirit. So, the three of us set up the company. It operated for some period of time, with about a half-dozen people.

Hughes: Where was it?

Rutter: It operated in a space contiguous with Hana Biologics, which is a small company controlled by Charles Crocker, a son of the Crocker banking family

[2] The Urdea oral history is found at http://bancroft.berkeley.edu/ROHO/projects/biosci/oh_list.html

and an investor. But Hana also had other investors, an Italian company, Riccordati, which also was interested in technology, and others. Hana was focused on biology, that is to say, the commercial aspects of cells—cell culture, media, that kind of thing. Our labs were contiguous. We met Charles Crocker, that is to say, I met Charles Crocker on various occasions. He was a classmate of Ed Penhoet's wife, Camille. We thought that their company, Hana, and Biopolymers could aggregate services and therefore make a stronger company. Gordon Sato, a friend of mine from UCSD and a distinguished cell biologist, was the major contributor on the cell side. Gordon's subsequent career shows how entrepreneurial he really is, an extraordinary person, for sure. He was kind of the scientific figure and impetus for forming Hana, and he contributed the name, as well. (Hana is Japanese for flower.) So, after a period, the two were integrated in the same company. It became evident that the company itself was complex. The business model for services was a difficult one, and there were stronger competitors out there. Eventually, when we formed Chiron, we purchased that group from Hana, because we needed the synthetic capability within Chiron.

Hughes: Just that group?

Rutter: Just that group.

Hughes: Were there others?

Rutter: They included, besides Mickey, James Merriweather, who worked for Chiron for many years, and several other people who worked for them, particularly Cathy Steimer, a very fine cell biologist and important scientist at Chiron, and two or three other people. Because of our setting up Chiron, also in somewhat contiguous space in the same old buildings in Emeryville, we were be able to attract many of the best people from Hana, including Tony Brake's wife, who was a key employee at Chiron for many years. As a result of that, I soon became persona non grata with Hana—

Hughes: For stealing people, you mean.

Rutter: --and left the board unceremoniously.

Hughes: You left or were you given a little shove?

Rutter: It was not a shove—a shove is a de minimus term. We didn't at all take their core technology or usurp their research or business plans, but the business, it was already evident, was in trouble. So people began to come to us for employment, and they were good people.

Hughes: Genentech was up and running, and they were working hard on somatostatin. One of the technologies that got them to their goal was their synthetic DNA

capability, first from [Arthur] Riggs and [Keiichi] Itakura, and then Roberto Crea came on board. Is that what Hana had, that same capacity?

Rutter: No, Hana had no ambitions for creating a gene factory. They had no ambitions for getting into molecular biology, to my knowledge. They had a small service business which was associated, as I said, with mammalian cells. Gordon Sato was a mammalian cell biologist. So no, Hana did not have that kind of an ambition. On the other hand, Chiron, for its own work purposes did have that ambition, and I'd say any biotech company that was interested in DNA/RNA technology had to have synthetic capability because those compounds were not available commercially at the time.

Hughes: And did that technology come from the group that you had bought from Hana?

Rutter: Yes, both Mickey Urdea and Jim Merriweather came, but we hired others as well. Now incidentally, Charles Crocker was a founder of Chiron, so we weren't disadvantaging Charles Crocker; we were advantaging him. As it turned out, he was ostensibly supposed to provide commercial know-how, financial and business know-how, to a couple of acolytes. That transfer of knowledge never occurred; he never played a role.

Hughes: Wasn't that self-defeating if he had invested in Chiron?

Rutter: Well, he certainly made a lot of money out of that initial investment in Chiron. A lot of money! So, I don't know how he thought about it. He had only the most superficial understanding of anything we were trying to do and didn't really try to find out.

Hughes: My understanding of one of the roles of the VC [venture capitalist] is to provide business knowledge for the initial years of a company. And since he wasn't doing that, he was taking a certain risk, I would think, just in terms of his own investment. The company was run by two scientists [Rutter and Edward E. Penhoet], and what did they know about business, one could argue.

Rutter: He might have felt he had a conflict of interest with Hana, which was, after all, an ongoing commercial organization with other investors. I don't know what he told them. He wasn't just a VC; he was a founder—he participated in the initial founding of the company! He invested $100,000, as did Ed and I.

Hughes: So he had founder's stock?

Rutter: Yes, he had founder's stock. So I was disappointed, truly disappointed. Honestly, it was quite a learning experience. In retrospect, we didn't define his role and our expectations in legal terms.

Hughes: Well, there are two more steps as I see it. One of them is the interesting conversation that you had with Bob Swanson and Kleiner Perkins [Caufield & Byers] about the possibility of joining Genentech. Can you tell us that story?

Rutter: This occurred in parallel to Genentech's program on insulin. They were working on a project to synthesize insulin in bacteria via synthetic oligonucleotides coding for the amino acids of the two peptide chains, (which were known). Simultaneously, our labs, that is Howard Goodman's and my [UCSF] labs, were involved in the cloning of the complementary DNA of the insulin gene, which is derived from the natural sequence of the insulin messenger RNA. This sequence potentially could be translated to form pro-insulin, the natural precursor of insulin, with its own intrinsic folding capabilities—a very efficient, first-order reaction. It seemed perfectly obvious to us that synthesis of insulin via the two peptides which comprise insulin would require them to fold in a second step, and that process was likely to be inefficient, as in a second-order reaction. The chemical process itself also had many problems. So when the cloning was proceeding well, and after it was successful, then we had serious discussions with the Genentech group about joining them.

Hughes: This was rat insulin, right?

Rutter: Rat insulin, yes, but human insulin would come very quickly after that.

Hughes: The cloning of rat insulin by the Rutter-Goodman team was announced in May of 1977.

Rutter: That's correct. It occurred that spring.

Hughes: Do you think that was probably a prompt to get Kleiner Perkins's attention?

Rutter: Well, for sure it was an important signal because then it was obvious that human insulin could be obtained by similar methodology, though significant barriers still existed.

Hughes: So probably it was in that 1977-78 time framework that these negotiations with Kleiner Perkins were going on?

Rutter: That's right. And they weren't exactly negotiations. Well, I guess they were negotiations. That is to say, we were trying to establish some kind of basis for working together collectively.

[Tape 2, Side A]

Rutter: In the end, we wanted equal shares for the two of us. We discussed a modest share of the company, five percent I believe at that stage. Of course, we did not know the percentages held by Bob [Swanson] and Herb [Boyer]. We even

attended a Kleiner Perkins business meeting involving all of the companies they supported—everything from tennis shoes to biotechnology.

Hughes: Was Swanson there?

Rutter: Oh, of course. Swanson and the whole crew were there. Herbert Boyer, Keiichi Itakura, Arthur Riggs, Howard [Goodman], and I. Subsequently, those talks drifted, with no real action taken by Bob, and I think the decision was simply not to go ahead. We honestly never spoke about it after that with Bob or Herb.

Hughes: Do you think the crux of the matter was that in their opinion you were asking for too much money?

Rutter: I have no idea about that. It wasn't money per se; it was equity. But it was a modest amount of equity, I thought. I don't think it was extraordinary, and further there was no negotiating. I think they simply didn't want the complication. Genentech was about more than insulin. But our (my) interests were broader as well. I think it might have been an organizational issue. I was used to running the department, and was pretty strong-willed. Nevertheless, I would have willingly supported Bob as the CEO. Howard was also very strong-willed.

Hughes: It may have been at a time when Swanson and crew knew that their way of going about the synthesis of human insulin was going to work, and so why did they need you with the complementary DNA approach.

Rutter: Well, that could have been one of the reasons, but the advantage of the approach via proinsulin was obvious.

Hughes: There was still growth hormone to come.

Rutter: Well, growth hormone would have been part of the deal. That would have meant including John Baxter.

Hughes: That's what I mean. You and Goodman still would have been attractive, one would think, from the science you could bring to Genentech.

Rutter: Plus all the rest of the projects. So it would have made a very significant addition to the technological competence and biological and medical perspective. On the other hand, I believe that the relationship of Bob Swanson and Herb Boyer was very strong, and they managed the company. I believe that that simple, coherent management would have been altered by the addition of Howard and me, no question at all about it. My guess is that that's the part that didn't work for those guys.

Hughes: Well, I can see how to a twenty-eight, twenty-nine-year old Swanson, you would appear as a considerable threat.

Rutter: I didn't necessarily think of it as a threat, but it's for sure that I wouldn't have been pushed around, and his authority was virtually a hundred percent under those circumstances. That kind of coherent management is good in a company—just take a look at what he accomplished. So no doubt, Kleiner Perkins, particularly Tom Perkins, raised those issues with Swanson and Boyer: do you want this complexity or not? That's my guess. All of those meetings occurred after the cloning of rat insulin, not before. As I testified before the Adlai Stevenson committee of the US Senate, they asked explicitly, "Did you have commercial intent doing those experiments?" The answer was no, absolutely not. At least, I had no commercial intent; the experiments had to do with my interest in the pancreas. But on the other hand, once the cloning was done, it was obvious there was a commercial intent since several companies came our way wanting to acquire the technology. So there was commercial interest and quite a transforming experience. So yes, it was an epiphany.

Hughes: By late 1978, early 1979, the two postdocs, Axel Ullrich and Peter Seeburg, had agreed to join or were already at Genentech. So another argument could be that in these two individuals Genentech had part of the technology that UCSF had developed.

Rutter: Well, yes. I think Genentech developed a clever strategy of bringing in young people. I'm sure that was under discussion, too: why not just bring in the guys that really do the work? They [Genentech] felt under the circumstances, probably with the acquiescence of Ullrich and Seeburg, they could just transfer the technology, and everything would be hunky-dory, and there wouldn't be any consequences. The subsequent history reflects that, obviously. They thought they were getting everything for one million dollars, and the university (and I) thought they weren't.

Hughes: This situation much later became a basis for a huge law case.

Rutter: Yes.

Hughes: Is Amgen the next step in the story?

Rutter: Well, yes indeed. That is to say, any commercial development of Rutter-Goodman technology through Genentech was essentially put on hold, because obviously it was going to go nowhere. And since the development lab was impractical, I had too many interests, non-insulin interests, that were of a commercial nature. These included hepatitis B. We started immediately on that program, and there was an intense program supported in the university by Merck. Eli Lilly supported an independent program on insulin in UCSF biochemistry, obviously a backup program from their standpoint in which

they wanted to essentially obtain whatever they could from the university, playing both sides to win [ie. supporting both Genentech and UCSF research on human insulin]. At that point, I had no interest to set up a company by myself—that would have eventually taken away my commitment to UCSF. So I accepted the invitation to join the scientific advisory board of Amgen.

Hughes: Did that invitation come from George Rathmann? Was he on board yet?

Rutter: No. Amgen was a unique company started by investors. The invitation came from— [pause]

Hughes: Salzer?

Rutter: Winston Salzer, who had obviously been thinking in these [commercial] terms. He was an entrepreneurial scientist who had not contributed fundamentally to the technology but understood its future. So he had been chosen to lead that company, and he persuaded a lot of good people to come and be advisors. It was a great group. I joined that group enthusiastically and introduced them to my interests and general ideas about targets, which were growth factors and hepatitis B. Both became programs at Amgen, and I strongly supported the people in the company. I had known the work on a factor called erythropoietin, as it originated at the University of Chicago in Eugene Goldwasser's lab. I was quite friendly with Gene and had spoken with him many times about this interesting project. He had no ability whatsoever to isolate a large enough amount of the compound to really define the range of its biological activities or its chemical structure—let alone use it for treatment of human beings. So I strongly urged Amgen in the area of growth factors to take a look at Gene Goldwasser's program. Interestingly, Gene was never considered to be "distinguished" enough to be a member of the scientific advisory board. Incidentally, I remember that people were very skeptical about the market for erythropoietin. Most of the people thought that it had too small a market and therefore was not an attractive target.

Hughes: How could they think that?

Rutter: Well, it's like many novel products; you never really know what the value of the target molecule is until you find out what it does in people, and then you discover all kinds of uses and also unwanted side effects.

Hughes: At that stage, erythropoietin's use in connection with cancer wasn't particularly thought about?

Rutter: Yes, I think that's right. But the work on hematopoiesis was well known as a result of the work of Till and McCullough and collaborators in Toronto, so this was a real rich field. So I was really hot on that, plus other growth factors and hepatitis B. Eventually Winston was replaced by George Rathmann.

George brought a lot of wisdom and dynamism—wonderful guy and a great CEO, a great future for Amgen.[3]

Hughes: Would you say when you look at the biotech pioneers that he was unique in having almost equal measures of scientific and business experience and sagacity?

Rutter: Well, I don't know about equal, but he was very unusual in being a well-rounded scientist. I believe he got his degree in physical chemistry.

Hughes: Yes, he did, from Princeton.

Rutter: He worked at 3M. He had this physical-chemical background, and it was quantitative, so he had a very sound scientific background, and he coupled this with great personal skills and savvy.

Hughes: George told me that Amgen's Epogen program eked along for a number of years, with his personal endorsement and the Amgen scientist [Fu Kuen Lin] doggedly pursuing the project.

[Tape 2, Side B]

Hughes: What happened to the invitation to join Amgen's scientific advisory board?

Rutter: I was on Amgen's science advisory board, as I mentioned, but was not totally happy because of my own scientific and medical interests. Well, it came down to the fact that Amgen was involved in so many things that they were unable to focus on the projects that I liked, projects that I was committed to. Hepatitis B was one of them, and it was probably the precipitating factor [for my departure]. But in addition to that, I was interested in IGF-1 [insulin growth factor-1], still interested in insulin, but in other growth factors as well, EGF [epidermal growth factor] and nerve growth factor (NGF) among them. I thought a whole range of growth factors were important. At that time, Amgen was pursuing projects as diverse as the synthesis of indigo, recapturing of precious metals from mining, commercial bacteriology, and so on. At the same time, they had a program with Marvin Caruthers on nucleic acids, prior to the spin-out of the group that eventually ended up as ABI [Applied Biosystems] with Sam Eletr. Lee [Leroy] Hood was also a member of the scientific advisory board, and because of his wide interests, there was contention over how much technology and programs would be inside Amgen and how much would be developed external to it. I was personally a proponent of keeping the company integrated, because at that time the technological diversity and scientific strength was the best in the industry, in

[3] Rathmann's oral history in this series is found at:
http://digitalassets.lib.berkeley.edu/roho/ucb/text/RathmannBook.pdf

my view. But the VCs in their wisdom decided on making a separate company [ABI], and I could see in the end that was also a wise decision.

Hughes: You mean Amgen North?

Rutter: No, I'm talking about the split off of Sam Eletr and the DNA technology with Marvin Caruthers in Colorado.

As I mentioned, Amgen had a diverse range of projects with only limited financial resources. Of course, each one of the projects had their own proponents. I naturally wanted to become directly involved in some projects, because some of the projects faced heavy competition, particularly hepatitis B. So I made the proposal to set up Amgen North. George explored this possibility vigorously. He came up to San Francisco and visited with Ed [Penhoet][4] and Pablo [Valenzuela], whom I'd introduced separately as candidates for director of research of Amgen. George was interested in recruiting them to Amgen. I am not sure at this point which he preferred, but the prospect of losing either of these colleagues gave me heartburn. This was particularly acute with Pablo, with whom I had worked for a decade. We had formed a great productive team. I knew that if Pablo left, the productivity of my [UCSF] lab would suffer.

While that process was maturing, the competition in hepatitis B was accelerating. Pablo played a major role in that project. I think the turning point came when I attended a Battelle [Memorial Institute]-sponsored meeting in Washington, D.C. To my surprise, it was a meeting that was attended as much by venture capitalists and bankers and commercial people as scientists. I felt that we didn't have sufficient resources to be competitive in our projects, particularly hepatitis B. So I called Roy Vagelos at Merck in Rahway, New Jersey and asked him if I could come up and see him. I outlined the reasons why it was important to move our hepatitis B project out of the university if we wanted to win the race of characterizing the hepatitis virus and developing the vaccine. Otherwise, I thought it was quite likely we would lose Pablo. He was crucial to our scientific productivity. I wanted to keep the UCSF hepatitis B team together, and we could do this independently, perhaps more effectively, than with Amgen South. In the context of forming a strong partnership with Pablo, I agreed to split with Pablo any personal revenues obtained from patents derived from the UCSF research on the hepatitis B project. The proposed budget for Amgen North was not large enough to support this group and my favorite projects. So that made the decision simple—if Merck would agree to sponsor an arrangement in a separate company.

[4] Find an oral history with Penhoet at:
http://digitalassets.lib.berkeley.edu/roho/ucb/text/regional_char_of_bio.pdf

In the prospective company, I wanted to have Pablo and Ed Penhoet. Ed was a very bright, articulate person, one of the most talented teachers at Berkeley but whose research projects were perhaps not as distinguished as he and the Berkeley Department of Biochemistry would have liked. Ed was a natural collaborator—a person who loved to work with others, and one who supported and enhanced the research of those around him. In that sense, he was a born leader of a research organization. Those talents were not fully appreciated or utilized at Berkeley, and Ed told me he was enthusiastic about considering another career.

Of course, George was not blind. After I introduced him to Pablo and Ed and mentioned their respective talents, he actively tried to recruit each of them to Amgen. Of course, Amgen was an ongoing concern with considerable financial and research resources and could make a compelling offer. I countered by suggesting that the three of us found a new company, anchored by the hepatitis B program and the insulin programs. By this time, Howard Goodman had accepted an offer to be head of a research institute at Harvard, funded by a German pharmaceutical company, and he no longer was a factor to be considered. Happily, Merck became enthusiastic about the concept. With Roy Vagelos's support, we looked rapidly to find out if there was some space in one of Merck's companies. There was a local one, a little chemical facility, which was not acceptable, and another chemical plant in San Diego, which was not appropriate either. So we had to start in a new facility. Merck agreed to underwrite this hepatitis B project with a contract. With that, we decided to go ahead and not further negotiate with Amgen.

Hughes: You mean, go ahead and found a company of your own?

Rutter: Go ahead and form a company and not further negotiate with Amgen, which obviously was going to take a long time and resources and a big time commitment. Prior to that, as I mentioned, I'd suggested both Ed and Pablo as candidates for director of research, and George had met them both and was very strongly positive to both of them. So it became obvious as well that if I didn't coalesce the group to form this company, one or both of them would leave. That led to several meetings between the three of us. I'd known Ed for more than fifteen years and Pablo for more than ten, and I had worked with Pablo all that time, so they were people that I knew well, trusted, respected, had great affection for. Ed was a Ph.D. student of mine, and Pablo began as a postdoctoral associate.

So over Easter weekend [1981] Ed and I got together to write a business plan. I wrote the draft, I still have the pages in my handwriting. Ed and I talked about the concepts. It was really not a business plan; it was a research plan, outlining projects. That was the basis for the start of the company. We initiated it on capital put in by Ed, and later by me, and still later by Charles Crocker. I think we each put in a hundred thousand dollars. That's how Chiron got started.

Hughes: How did [Jean] Deleage come into the picture?

Rutter: Well, three hundred thousand dollars doesn't do too much, and we were screwing around trying to get labs on the most economical basis possible. We started in the same building as Hana, but soon found an old dilapidated building that had been part of the Shell Research complex [in Emeryville], but long since abandoned and inhabited by owls, piles of bricks, and an itinerant or two. We constructed our own laboratory benches in a quite basic but serviceable facility. As I mentioned, we needed resources, and none of us knew very much at all about business. How is that for a beginning?

Hughes: Had Crocker also put a hundred thousand in?

Rutter: Yes.

Hughes: That was all that he ever did?

Rutter: That's all he ever put in. Smartest move he ever made. I honestly believe that. Ed had a respected family friend who worked for Spinco, I believe. His name was Morris Hannefin. We went out to see him. He was kind of an advisor about how to set up companies and what you had to be worried about, stuff like that. We went through the process: it was simple to set up and easy to initiate, and we decided to move forward.

That was the easy part. We tried for some time to learn about sources of funding. Neither of us knew anything about venture capitalists or venture capital. We eventually had some discussions with Sutter Hill Ventures, with Leonard Baker and David Anderson. I think they weren't awed and didn't seem too enthusiastic, or at least they were kind of negotiating a low value, as I recall.

But we met Jean Deleage in another way. At some point, when I was with Amgen, there was a meeting with potential investors in San Francisco. George could not make it for some reason and asked me to represent the company. After the presentation, Jean walked up to me and said something like, "If you ever want to start a company, come and see me." I decided to look into it. One of the people in my lab, Raymond Pictet, who was Swiss-French, also knew Jean Deleage and brought him to the lab to "get acquainted."

[Tape 3, Side A]

Rutter: I remember well—I think it was on a weekend because no one else was in the lab—Jean Deleage came over, sat down on a laboratory stool. We talked about projects that interested us, what the business plan was, and so on. He made a decision to support us in a couple of days. I think he invested a million or a million and a quarter dollars.

Hughes: Had he invested in biotech before this, or anything biological?

Rutter: He was part of an investment partnership, Burr, Egan, Deleage & Co, that had broad interests. But Jean was interested in biotech. They frequently invested in concert with other French investors. Part of the pitch they made was that they had call on a lot of French money and it would be easy for them to get money and establish business contacts in France. So in this sense, they supplemented our own contacts, and they could help develop the business. Along those lines, they certainly facilitated many trips to France, and we met with key figures in the pharma industry and the oil, petroleum industry—many wonderful dinners.

Hughes: Did any business result?

Rutter: No contracts, no contracts.

Hughes: Why do you think that was?

Rutter: Well, there were several reasons, mostly related to the fact that this [biotech] was a novel, unproven field. But we came dangerously close to getting a contract with Sanofi. There was an internal fight between two sectors of the company. One group wanted to produce a product by bacteria, the other by mammalian cells. We could do it with yeast. So the general idea was, instead of choosing one group or the other, they would choose still a third—that was the reason for our negotiation! [laughter] I think they didn't know quite what to do with biotechnology. They were so involved with their own structure. I'm not sure whether there was any strong collaboration by any biotech company with a French company.

Hughes: No?

Rutter: Not that I can recall. So I think maybe it was just a characterization of the French industry as it existed at that time.

Hughes: Therapeutic Biopolymers was the original name, but within days there was a name change to Chiron. Do you want to tell the story of how the name Chiron arose.

Rutter: Yes. Well, in the industry there was a tendency to use technical names instead of a heuristic name or an iconic name. There was Genentech, and there was Amgen, and so on. I think I had come up with this name Therapeutic Biopolymers, but it sounded very uninteresting. I think that someone said, "That's a kind of stodgy name. What are we going to do about it?" I agreed immediately, I believe, because I recall suggesting that we search in the Latin or Greek for one of the legendary figures that had something to do with medicine. We were discussing that kind of approach, I think, at Ed's kitchen table or in some kind of home environment—it wasn't mine—and we left with

that notion. Then Ed began talking about this with his children, and I think Braden, his second son, was in high school and studying Greek or the classics. He came up with the name Chiron, among other alternatives. Of course Chiron was an "a-ha" name; it was perfect in the way we thought of ourselves, and we were delighted with it.

Hughes: Let's talk about the recruitment of staff, maybe first the scientists, because I presume they came first. Did the scientists from Hana come immediately?

Rutter: No, they didn't come immediately; they came later.

Hughes: Who were there first?

Rutter: Primarily the group from my lab, Pablo of course, along with the technicians who worked with him.

Hughes: Graeme Bell?

Rutter: We eventually recruited Graeme Bell, who was the person responsible for the cloning of the human insulin gene, a marvelous technical person and extremely intelligent--now a distinguished professor at Chicago. [R. A.] Rob Hallewell came from Howard Goodman's lab.

Hughes: Was he a postdoc?

Rutter: Yes, he was a postdoc. Leslie Rall was one of my postdocs. Come to think of it, I honestly don't remember if Leslie was a student or a postdoc. George Kuo was another very talented researcher that I knew at UCSF. George came from another department. He came to see me about a job, and we were delighted to have him join us. Then Ed began recruiting people from Berkeley. Steve Rosenberg was the main person that I recall.[5] So the initial group was largely recruited from my lab.

Hughes: Was Michael Houghton part of that original recruitment?

Rutter: No, he came later. He worked at Searle in England, and we recruited him after we had some success with the hepatitis B vaccine project and were starting to build the research team. He was not recruited for a specific project.

Hughes: So that was a little later?

Rutter: Yes, significantly later. We worked as a research group, much as I ran my [UCSF] lab, with strong operational leadership by Pablo and strategic leadership from me.

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[5] See the oral history with Rosenberg at:
http://digitalassets.lib.berkeley.edu/roho/ucb/text/rosenberg_steven.pdf

Hughes: Do you have any recollection of when the Hana group came over? It was probably dependent on when facilities become available because at first you had only two small labs that you rented from Hana.

Rutter: That's right. So after the money came in from Jean Deleage, my guess is.

Hughes: Which was '82?

Rutter: A year, few months, something like that [after founding Chiron in 1981]. Initially, there was a separate corporate office in downtown Berkeley. Ed worked together with Suzy Sanders, wife of Tom Sanders. Tom Sanders also was a previous student of mine and joined us as one of the early employees.

Hughes: As a scientist?

Rutter: As a scientist. He had been an assistant professor at Princeton but didn't make tenure there. Then he left to take on a role in a college north of Chicago, and he left that job to come to Chiron.

Hughes: I have a feeling that he took on more than science at Chiron.

Rutter: Tom was very bright, multitalented. If we wanted to learn something about a subject or field, any field, Tom was the go-to guy.

Ed and Suzy and Pablo looked around, and then we rented some space from Hana and then got our own space in the building across the way which we did have to renovate. Most of the laboratory benches were constructed simply and extremely inexpensively by a contractor who worked for us. C. K. Chang, who had been head of laboratory resources (chemical stores, etc.) in the department at UCSF and separately an entrepreneur, played a similar role at Chiron.

[Tape 3, Side B]

Hughes: Did you have the contract with Merck yet?

Rutter: Merck agreed on a contract, and contemporaneously with this development we negotiated that contract through Brobeck Phleger & Harrison LLP. The senior partner was John Larson, but we worked directly with Bill Green. I believe initially it was for two million dollars. Later, we persuaded Bill Green, who was a friend of Ed Penhoet, to come on full time.[6] The contract supported the work of half-a-dozen scientists, I think. After we looked at various alternatives, we set up a cooperative program with Ben Hall [at the University of Washington] to do protein expression in yeast. We had tried extensively in my lab to get significant expression of the hepatitis B surface antigen in

[6] See Green's oral history at: http://digitalassets.lib.berkeley.edu/roho/ucb/text/green_william.pdf

bacteria, but failed. We had worked with yeast before, and were convinced it was a better expression vehicle. We decided to use yeast because we wanted to produce a mimic of the hepatitis B particle, twenty-seven nanometers in diameter, which was seen in the serum of infected patients. Yeast was a eukaryotic organism, and it had similar cellular structures to those in mammals. I had recruited an outstanding yeast biochemical geneticist, Ira Herskowitz, to UCSF. (In fact, we asked Ira to be a consultant to us [at Chiron], but he declined.)

We used yeast in my lab at UCSF but did not have a strong yeast promoter that could be used to drive the expression of a transgene on a commercial scale. So I sought promoters everywhere in this country, including from a former postdoc, who was then at UC Davis, who had been studying expression in yeast using various promoters for the enzymes used to break down glucose to eventually produce alcohol. Mike refused. I talked to all the likely sources of promoters from various labs all over the country. All refused to give me their promoters or refused to collaborate; they were all affiliated with one group or another. Ben Hall, who had been a colleague at Illinois and also at the University of Washington, was working on expression in yeast. We finally made an arrangement in which he and his colleague Gustav Ammerer would obtain a full 50:50 share of the experimental result from the experiment. A very tough negotiation, but we finally could get on with it.

Hughes: Their system included a promoter?

Rutter: The key ingredient was the promoter that could be coupled to a transgene—in principle. Ben had been working on alcohol dehydrogenase and other yeast promoter systems along with others at UW. Incidentally, he also had been working with Genentech. So Ben was negotiating with both Genentech and ourselves, and he insisted on being a major player in our hepatitis B program for having provided a promoter, a component of the expression system. The combined project was carried between his lab and my lab, that is to say, the work was carried out by Pablo and Ben's colleague Gustav Ammerer.

Hughes: Genentech dropped out of the collaboration?

Rutter: Genentech was never in collaboration.

Hughes: It was just a possibility—

Rutter: It was a possibility for Ben Hall to work with them. Then Ben, unbeknownst to me, established a relationship with Merck, tried to get Merck to support his program at UW and a company. For the first time in my life discussions on a collaboration started with a telephone call with attorneys and ended with attorneys. So we made an agreement between the University of California and the University of Washington on the first experiments. After Chiron was formed, another agreement with UW was formed. We did the key experiments

in Chiron, but they were anticipated by the work at UCSF, and the University [of California] and the University of Washington get royalties.

Hughes: Yes, tremendous royalties, right?

Rutter: From what I gather, the hepatitis B royalties have been the highest of any patents in the UC system for about a decade.

Hughes: I've never seen that agreement with Merck. Do you remember in outline some of the parameters?

Rutter: This was a specific agreement in which the royalties would be shared fifty-fifty between the two institutions [UC and the University of Washington]. The royalty is a couple percent for both institutions, so both institutions have really done very well.

That agreement had occurred just prior to Chiron getting started, so a major aspect of this was the role of Chiron in the further development. Of course, it was a very significant project within Chiron. The two universities had a research agreement with Merck, and with Chiron it was a contract. The aim was to produce particles that mimicked the hepatitis B particles. The first experiments at Chiron, carried out in the first few months after we had laboratories, demonstrated that we produced in this system hepatitis B antigen as detected immunologically, and we also could see particles in the microscope! These were amazing results—the first complicated structure naturally made in humans but produced by genetic engineering in a foreign—microbial—cell! We were all elated by these results obtained in such a straightforward experiment! I specifically remember the conversations with Ben—both of us were conservative in drawing conclusions—saying that we would really know what we have only when we see the electron micrographs. Sure enough, there were particles, beautiful particles—smaller than the particles that were normally produced in humans—twenty-two nanometers, instead of 27 nanometers—probably due to the size of the surface antigen employed and also perhaps the less adventitious binding of other molecules. In the end, despite its complexities, we had a successful collaboration, a fundamental lesson in getting things done in a competitive and personally complex environment.

Hughes: The particles worked as well as the natural ones?

Rutter: Oh, they worked beautifully in the production of neutralizing antibodies. They're the basis for all the hepatitis B [vaccine] made in the world today, and still [using] the same basic technology. The results were so clear cut that it resulted in a major project within Merck. At first, it was controversial because Merck had their own hepatitis B project, developing a vaccine based on the non-infectious particles from infected individuals. Maurice Hilleman had championed that project.

Hughes: He was a forceful individual, was he not?

Rutter: He had a very forceful personality and managed projects with great intensity. I had a really nice letter from Maurice a couple days ago, and if I can find it I'll show it to you. But, at that time, he was defensive of his own program and skeptical of ours, so it required Roy [Vagelos], at that time head of Merck Sharp and Dohme (Merck Research) and later Merck CEO, to support this project. Subsequently, Pablo participated directly in the development of a commercial process at Merck laboratories. Ed Penhoet adroitly managed the relationship.

Hughes: Was there already worry about Hilleman's method, which depended on human sera, and the potential for infection?

Rutter: No. All this was prior to the discovery of HIV, and infected serum was not a big worry at that time. However, the use of serum from infected patients for control of an infectious disease was of its own nature a self-limiting process. However, the discovery of HIV did totally transform the project. It completely eliminated the other [Hilleman's] way of doing it, and of course exacerbated the need for such a vaccine that totally eliminated the possibility of infection from the vaccine itself .

Hughes: Did the Hilleman method disappear before HIV was isolated [1983]? There was evidence before that, of course, that people were getting AIDS from blood transfusions.

Rutter: Well, yes, indeed. But still, at the time of the development of this in the early eighties, that was not very well known or established. Indeed , the blood-based vaccine was developed and sold for a time, but it was completely superseded by the yeast vaccine. Pablo went numerous times [to Merck] and transferred the laboratory process to the relatively small facility used for scaling up the process at Merck. I believe that facility was used for several years for commercial manufacturing.

Hughes: Was it always Chiron's expectation to sell the technology? Could Chiron have kept the technology and supplied just the particles, for example?

Rutter: We had no capability of manufacture on a large enough scale at that time, though if there were no Merck contract, we could have developed the process. However, the facility itself would have taken considerable time and resources to build, and of course after that there would have been the problem of obtaining FDA approvals.

Hughes: I know that. But you could have been worried that Merck would appropriate the technology.

Rutter: What technology?

Hughes: The actual manner of producing the particles.

Rutter: We demonstrated how to do it in the laboratory. And we transferred it to Merck.

Hughes: I asked the question, thinking of what earlier had happened with the insulin and growth hormone projects. One claim in the lawsuits was that Genentech had never intended to supply Eli Lilly with the technology; it was only to supply them with the two insulin clones for the A and B chains. In other words, Genentech wanted to hold onto the technology and supply just the rudiments of the product.

Rutter: The rudiments of the product, meaning in this case the peptides?

Hughes: Yes.

Rutter: So they were doing manufacturing?

Hughes: Genentech wasn't going to do manufacturing. My point is, Genentech was struggling to hold onto the technology itself, and only supply the rudiments of the insulin product. You couldn't do that in the case of hepatitis B?

Rutter: I didn't quite understand that, Lilly had to manufacture, and in order to manufacture, they had to have bacteria.

Hughes: Yes, and Genentech supplied the clones that had the two insulin chains.

Rutter: So did we. So they licensed the use of those clones for that project. The technology was not licensed, except the ability to produce hepatitis B particles.

Interview 2: September 18, 2004

[Tape 4, Sie A]

Hughes: Dr. Rutter, we have the first business plan available.

Rutter: What was it?

Hughes: Well, there were two. There's the handwritten plan that is really more a scientific agenda that you wrote at that Easter meeting. Then sometime later, maybe many months later, there was a formal business plan, which I don't believe had the date, but I'm figuring it had to be 1992. It was written ten months after the handwritten version, and it's quite different. So with that in mind, I thought we should talk about how the business itself was organized.

Rutter: It's strategy, then.

Hughes: Well, yes, and also corporate organization.

Rutter: So let's just talk about the business strategy.

Hughes: Well, before we talk about that, let's talk about business models, if there were any.

Rutter: In the industry itself?

Hughes: In your mind as you were setting up this company. Were you using any of your past experience? Ed Penhoet as well?

Rutter: Not really. I'd had experience at Abbott. I knew something about Merck, a little bit about [Eli] Lilly. But certainly my deepest experience was Abbott. But I would say the evolution of a business model in the context of planning the ultimate business was not something I knew much about or we knew much about and we didn't do it in that way. That is, we didn't build the company anticipating a marketing organization that would work in all parts of the world or where we would manufacture. Those issues developed over time with opportunities and with accomplishment. In some senses, this company, like most companies, grew like Topsy. The business of the company initially was research, pure and simple. That was the leverage we had. It was our "competitive advantage." We had technology that other people wanted, and therefore the issue was a combination of partnering and evolution to a business with our own products which ultimately would be sold by some mechanism. Presumably, the mechanism is still intact.

Each one of the companies mentioned here, that is, Genentech and Amgen, also grew organically in different ways. Amgen, at the time that we started Chiron, was trying to cover many different fields. It was a research

organization that was looking for areas that could be approached using their technology. In that sense, ours was much more focused. That is to say, we were really interested in infectious disease, and we were interested in growth factors, that is, using natural means to influence both disease and health. The goal was ambitious to be sure, but the strategy was clear enough. That is to say, in the infectious disease field a given line of research could be useful in several domains. Diagnostics was one of them, which had shorter term characteristics to reach the market, and if we chose the right targets, we felt that those targets could have a proprietary advantage in the field.

Hughes: You had that concept right from the start? Last time, I think it was probably off-tape, you spoke of leveraging from a common research base.

Rutter: Yes, that was the concept then. And that same kind of research could be used for therapeutics or preventatives. We were really describing then what is now characterized as a knowledge-based business. That's what it was. We had a technology base, and through that technology, we would accrue special information, knowledge which would allow us hopefully to control a field and through that establish a stable and successful business. The argument I made to myself was that diagnostics by and large was a nonproprietary business. All the tests were standard. They were in the public domain. And the business was based upon developing instruments to handle the tests more efficiently, with gradual improvement in sensitivity and specificity of the tests. So what effect would intellectual property have on a field like that? In a certain subset of the field, if one could get a test that was both high value and everybody wanted it, it would in a sense devalue all the other businesses that didn't have that test and then allow the ascendancy of a business which had it. So from a strategic point of view, the leveraging of the research was to develop intellectual property in all things that were important relative to a particular health problem and then build a business around that intellectual property and the new knowledge.

The same is true for vaccines. The vaccines which were then apparent were standard vaccines which had been around for decades and some for nearly a hundred years. If there was a new way of developing vaccines by molecular mimicry, as was the case with hepatitis B, that essentially eliminated all possibilities of infection by the vaccine itself because nowhere was the infectious agent present in the process. Only part of the infectious agent was present in the process, one gene or two genes or whatever. So that meant that with this new use of recombinant DNA technology to essentially provide a structure which mimicked the natural structure, one could obtain an immunological response which would neutralize the natural wild-type pathogen without danger. Well, that concept, a new concept I felt, would drive the field, and in a sense hepatitis B was the core demonstration of that approach.

Hughes: The core demonstration and also the core project upon which Chiron was formed, right? Without what your UCSF lab had previously achieved regarding hep B, Chiron probably wouldn't have happened when it happened. Wasn't your hepatitis B research and seeing its commercial value the push to found Chiron?

Rutter: We discussed that last time, and for sure it was. But at the same time, insulin was a paradigm for growth factors, and I was working on IGF-1, insulin-like growth factor, which is an intermediary in controlling growth, bone development, and lots of other things. And there were many other factors. We were working on nerve growth factor and epidermal growth factor as well, and it was just becoming apparent that these molecules might have powerful influences more or less like insulin had. So using these natural molecules to facilitate treatment of diseases or the extension of health was what we were thinking of. Each one of those areas, then, was different than the technology associated with the current business, so they represented a point of departure.

Hughes: The current business being—

Rutter: Current business in each one of those sectors.

Hughes: Including the fact—was this in your thinking?—that the existing biotech companies were not emphasizing these fields?

Rutter: Well, starting first with the pharma[ceutical] companies. The diagnostic companies were not doing fundamental research. They were simply developing instruments and tests according to a standard protocol, and they were associated by and large with pharma companies. Pharma companies were dedicated to small molecules. Nobody was interested in larger molecules except, obviously, those that were associated with diabetes, like Lilly, and there was a modest industry around growth hormone derived from cadavers and so on. The vaccine business was dispersed. Yes, there were companies like Merck, SmithKline, and Merieux, but most countries had small public health oriented vaccine organizations that had evolved from Pasteur's time.

It's interesting that roughly a hundred years ago when [Shibasaburo] Kitasato in Japan, Emil von Behring in Germany, and Achilles Sclavo in Italy started their vaccine programs, they became public health programs. The good thing about it at that time was that they were adopted by the countries, and each one of the countries was sort of on its own to develop these approaches to control disease. But in the ensuing hundred years, these became inculcated into the general activities of the governments, and so there was no novelty. There wasn't research going on to improve and change, so they languished. That is, that industry languished. There were only a couple of companies—Merieux in France was one—that were avant-garde. They were really trying to advance the vaccine field and develop an international business.

Hughes: Doesn't the Salk polio vaccine enter in here, too? My understanding is that in the wake of the Cutter Laboratories disaster when there were a number of lawsuits against the makers of the vaccine, companies began to be skittish about a vaccine business because of the potential for lawsuits.

Rutter: Oh, absolutely. This was the classical situation which set up the vaccine problem. Both were trying to solve a high-profile problem of worldwide significance. That is, the old way of making vaccines, whether they were killed or whether they were attenuated, always resulted in some people becoming infected. When the process was faulty, as was the case in Cutter, and large numbers of people got polio, then eventually it led to bankruptcy of the company. Some of the Cutter business was eventually taken over by Abbott, but they did *not* continue the vaccine business. The new strategy for doing vaccines, as I said before, eliminated that danger, plus the approach itself was general. If one could achieve mimicry broadly at the immunological level, then one could develop new vaccines against nearly everything. That was the general notion.

[Tape 4, Side B]

Rutter: I was certainly convinced that the methodology was translatable. I was more confident than I should have been that it was translatable on a case-by-case basis. Do you want me to go on with that right now?

Hughes: Well, maybe we should go back to the pure business part of the history.

Rutter: Each one of those three research areas had a scientific basis coupled to intellectual property for their existence. We thought that the pharma companies were weak in this area, both from a technological point of view and also they were not focused on these areas of opportunity among the biotech companies, there really wasn't a company that had focused on either diagnostics or vaccines, although Centocor did some of that.

[interruption]

Rutter: Most of these companies were project-oriented, that is, they would go after anything that was approachable. The question was, what was in sight? What were the available targets? I thought at least we had a fundamental strategy. The general idea was that the research program then could be leveraged and we could find partnerships, and out of the partnerships, the knowledge which would accrue would eventually allow us to enter all or a part of those fields.

Hughes: How much was your experience on the Amgen science board influencing how you thought about your own company, positively and negatively?

Rutter: Well, obviously, it was a significant experience, so we were more focused than Amgen was at the time. Amgen was supported in a major way by Abbott, and of course those guys knew what they were doing, I thought, and we were without significant business experience Still, I felt, just like running a lab, you've got to focus on what you're going to do in order to accomplish anything. We were interested in something broader than simply doing projects based on a technology—a specialty research house.

So after hepatitis B, we wanted to go further. What are we going to do in each one of these areas? What is required? What is going to be the next product which has relevance in all three fields, which is related to a public health issue, which would allow us to capture intellectual property and the knowledge associated with it, and therefore develop a sustainable organization out of it? I certainly didn't believe that technology per se was going to work for us. We had to work then to develop business and products that were based upon the use of the technology in certain fields. So in that sense, I was confident about the early strategy. For a research-oriented company, it worked well.

Hughes: You spoke several times of intellectual property concerns, and I know you had begun to patent out of your lab at UCSF. But if you were at all like most of your colleagues in the biological sciences at that time, you didn't have a long history of dealing with intellectual property concerns or even putting them first and foremost. Was it a given that if you formed a company, that intellectual property concerns had to be right there at the top of your consciousness? Or were you getting advice from Jean Deleage or Charles Crocker or whomever on the business side of Chiron that intellectual property protection had to be a major emphasis of this company?

Rutter: We were not getting advice from Charles Crocker or Jean Deleage on those matters. I would say that we certainly got advice from Merck in relationship to hepatitis B, but more than that, my long experience with Abbott had certainly made me aware of the necessity and power of patents in establishing a position based on your own work. It was perfectly obvious. In academic research, new findings are immediately repeated by others, who then go on to compete with you, in some way. The more important the work, the more groups get involved. Without intellectual property, it was obvious that research-oriented organizations would not be sustainable.

Hughes: Did you pay any attention to the fact that by the time Chiron was formed, the *Diamond v. Chakrabarty* Supreme Court decision was that living, manmade organisms were potentially patentable?

Rutter: First of all, I thought Ananda Chakrabarty had done a remarkable thing. He was and still is a very thoughtful guy, a very imaginative person. But to tell you the truth, I had never thought of patenting a natural organism. We were always talking about modifications of an organism for some utilitarian

purpose, and in that context, the utilitarian purpose, the commercial purpose, was the result of a creative act, and it had a right to be patented. That seemed reasonable to me. But for sure I was aware—who couldn't be aware?—of all the considerations and concerns.

Hughes: Well, the *Chakrabarty* case could have prompted you to pause and reconsider whether the time was right to form a company.

Rutter: I thought it was exactly the right time to form a company. It was the right time to form a company because I had great confidence we'd be able to do things that helped human beings. It was not an issue of damn the torpedoes, full speed ahead. This was an issue of understanding the potential of a set of technologies. My belief was that once that potential was demonstrated, most of the concerns would dissolve. To this day I believe if you take a pragmatic approach to the resolution of human problems via technology, one has to blast on past the issue that some ultimate, as yet amorphous situation may result which is in itself deleterious.

I think that there are so many controls that one has over biological systems that possible deleterious consequences could be satisfactorily addressed. The risks of the kinds of things we were doing, especially since they were all contained [by biosafety measures], were minimal, as compared to the problems in medicine and healthcare we were trying to address. Therefore the political and social issues were epi-issues to me. It was, however, a major reason why recombinant DNA technology was not adopted by the major pharmaceutical companies. They wanted to pay attention but keep it on the sidelines. They didn't want to become polluted by something that was controversial. After all, they were in the public market, and what would the response of the market be to these approaches? My guess is, recombinant DNA technology would have been *very* controversial at the board level. So it was totally appropriate that the young companies take it over. Well, that has been kind of my game in science and business. I mean, if you are trying to use technology to improve humanity, you have to use the most advanced forms of technology if it's appropriate, and not everybody wants to do that. Small companies are a way to make progress, and maybe the only way.

Hughes: What kind of outside help were you getting, if any?

Rutter: We were getting help largely from people who were interested in our technology. Certainly Merck. Merck was a great help. Despite the fact that they were quite distant from us, and we were just a contractor, still I knew Roy [Vagelos] from his academic days, and we had very straightforward interactions. I knew my colleagues at Abbott. I got no help from them directly because eventually they became involved with Amgen. But nevertheless that experience as an Abbott consultant was a meaningful experience. Then, while at UCSF, we had a relationship with Eli Lilly for a while. And so on. So all of those things helped. But frankly, I had no experience with running an entire

business. We were running a lab that had commercial potential, but it was an extrapolation of something that I'd done before in several different venues. It was a pretty easy extrapolation from a complicated department integrated within a medical school to develop a coherent program at Chiron with a group of focused individuals, especially with Pablo, who was just great as a colleague and practical thinker, and with Ed who was smart and was a great communicator and who had an innate sense of building an organization. He had demonstrated that at Berkeley. It wasn't the easiest thing in the world, but then again, it wasn't totally daunting either. I am glad we didn't recruit a person from "industry" to lead the effort. The culture would have been totally different, and maybe it wouldn't have succeeded

Then the issue of contracts and how the company worked, how we presented ourselves, well, that was in part an intellectual problem—

[Tape 5, Side A]

Rutter: —of establishing the right balance of values. In that context, the issue was the value of new knowledge and technology as opposed to money and experience. I took the view it was about equal, so fifty-fifty was about where to start. On the other hand, it was complicated with respect to contracts with Merck because part of the work had been previously done at UCSF, with the collaboration of the University of Washington, and so the royalties went in both of those directions. So, then, how much could Chiron get beyond that?

Hughes: Wasn't Benjamin Hall negotiating separately with Merck?

Rutter: Yes. I described that, I think, last time. Ben Hall, unbeknownst to me after we'd set up the program, also tried to get Merck to support his program independently of ours. He did get a grant from them, separate from our own contract with Merck. Frankly, I don't know all the details of that. But my supposition is that he tried to say that the approach to the hepatitis vaccine was a joint project, independently conceived, which was not true. They could have other projects going on. Neither Roy or Ben ever mentioned it.

Hughes: So Merck was dividing up the science and—?

Rutter: No, the science was integrated, but, as the authorship will show, it was a collaboration between Gustav Ammerer and Ben Hall with Pablo Valenzuela and myself. They provided the yeast, and we provided technology and the problem. So on the paper, it's fifty-fifty. Making the particles and then the vaccine, all that was done within Chiron. So, aside from those early experiments, then everything else was Chiron.

We had developed a model for royalties, but then when it all worked, Merck's chief negotiator, Edward somebody, had a meeting with Bill Green, Ed, and

myself. The pre-negotiated royalty was seven and a half percent. Ed [from Merck] kept telling us they were the only group in town that could bring the vaccine to the public market, so we couldn't possibly get seven and a half percent. He kept talking and offering lower and lower royalties until he finally reached half a percent! There were three of us: Bill Green, our attorney, Ed Penhoet, and myself. We were terribly deflated and glum. I said, "The heck with it. We're leaving." So we left. A week or so later, Ed [from Merck] called and said, "Well, Roy told me we'd better get this deal back. So let's come to a conclusion." We didn't get our seven and a half percent, but we got partway there, and this represented a major achievement and a step forward. All in all, Merck really helped us get started, and in that overall sense [the royalty] was fair, I felt. We learned a lot in the fire of negotiation, how negotiation was really carried out and, most importantly, the power of the organization that has the money and is doing the selling. It was a great lesson. High tuition, but a great lesson. We learned as we went along, mostly mistake by mistake.

Hughes: Were you at a disadvantage compared to biotech startups, such as Amgen and Biogen, which had experienced venture capitalists advising them? Or was the whole thing so new that everybody was learning on the fly?

Rutter: I think the advantage of Amgen and Biogen was that they had more resources, and, yes, their advisors no doubt helped as well. Undoubtedly, they had more to play with, and they had a larger number of people in the "executive" group and could carry out more programs. On the other hand, there was a real disadvantage, and that was the disadvantage that money brought and big corporate experience brought. I thought we were tremendously advantaged just because we were in control of our own destiny. We didn't have to ask anybody for anything, so we could make our own mistakes, and we made plenty of them. We could also make our own choices. So the strategy wasn't foisted on us by anybody, and Jean Deleage certainly did not. He was a supporter from the beginning. Outstanding venture capitalist and individual.

Hughes: Had he had any experience before with biology-based companies?

Rutter: Yes, but I can't tell you how many.

Hughes: What I'm trying to find out is, was there a learning curve for him, too.

Rutter: I'm sure there was, but I can't answer for Jean. But Jean has always had a sense of both betting on people and finding a problem that people could solve, and then supporting the program, and getting out of the way so they could work at it.

Hughes: Do you think that Deleage gave more independence than was true for most VCs?

Rutter: I can't answer that. Certainly he gives plenty of independence, and he's been very successful. He certainly didn't manage us. Well, he didn't have as much money in it, either. But he didn't manage us like Tom Perkins did Genentech.

Hughes: Or Moshe Alafi for Cetus.

Rutter: Or Moshe Alafi for Cetus. But I know little about that, really. If I know Moshe, they should have listened to him more intently.

Hughes: Do you think that some of the management style is based directly on the size of the investment? Or could it also be that Deleage—

Rutter: I think Kleiner Perkins was the sole investor in Genentech initially.

Hughes: The first time around, yes.

Rutter: And Cetus, there were several investors in it. When syndicates form, then you begin to crystallize a general set of business practices around it. But I can't truly make comparisons between these.

Hughes: I noticed in the 1982 business plan that there was a point made in the brief sketches of the three founders, that none of you was at the time associated with a university. The sketches made the point that you had taken a leave of absence and that Pablo and Ed had resigned their university appointments. There must have been a point behind that, or several.

Rutter: Well, there was a major point, and that is that in Biogen, for example, the key scientists were still university professors. We were making virtually full-time commitments to Chiron.

Hughes: Yes, I thought that would be one point. Was there also a residue of the unrest that had characterized the late seventies at places like UCSF of professors putting one foot into the commercial world and keeping the other in academia?

Rutter: Well, obviously, my (our) decisions were related to that issue. That's why I was saying that many of the other companies had part-time professors, professors who operated as professors but also had a company on the side. In our case, it was clear that we had made a commitment; we had changed. We were devoting the main part of our life to Chiron. Although I had an appointment in the university, I gave up my chair in the Department of Biochemistry and became a director of the Hormone Research Institute [at UCSF], which allowed me to do some research there, but also allowed me considerable freedom with respect to having direct responsibilities with Chiron.

It was only a matter of time when I would join Chiron full-time. I was simply not needed full-time at the beginning, in my view. I was still spending nights and weekends on Chiron matters, and my energy level was high, and I was able to get both jobs done. Further, my research, both at the technology level and on the problems I was addressing in my lab, better prepared me for my activities at Chiron.

Hughes: There's one sentence in the same business plan, quote, "Chiron is not a scientific start-up," and it's underlined. What else could it have been?

Rutter: Sounds a little defensive, doesn't it?

Hughes: In the very early days, wasn't it a scientific start-up?

Rutter: Well, it depends on your point of view about scientific start-up. Let me defend it. The notion behind that is that it wasn't just, okay, we'll have some science, and we'll have an idea, and let's go there. The fact is that we had really made progress, and even dramatic progress, on hepatitis B. So in that context, it was not a start-up with no specific project (e.g., like Amgen was). Secondly, we had the technology, which was transferred from my lab, predominantly my lab, but others as well. We had product categories, and we had a business strategy. So it wasn't something that was solely based on technology which was quite standard in those days. We had a level of experience and accomplishment in the field that we were trying to enter.

Hughes: As I said off-tape, the original handwritten document is quite different from the business plan.

Rutter: Can you stop that for a while, and let me just take a look at it?

[Tape recorder turned off.]

Rutter: I actually don't think that this business plan is substantially different, except it's an evolution from the general plan, which was laid out without specificity in that initial document. Here we provide specificity. We're still dealing with vaccines, we're still dealing with diagnostics, and we're dealing with therapeutics and commercial enzymes. In this case, therefore, we're talking about specific products and targets, estimated revenues.

[Tape 5, Side B]

Hughes: Well, understandably, the market projections certainly aren't in the first document. Was that something that you knew eventually you would have to deal with? Somebody had to do some research and get the tables together.

Rutter: Well, most of the tables, the selection of diseases and so on, were done just by perusing the literature and using documents that were already in the public domain. The target projections were all soft. They were done internally. We didn't outsource that kind of information. Of course it was important that we be orderly in our thinking of projects and in their extrapolation into the commercial domain. We had to present the case to potential partners, after all.

Hughes: Would Ed have been doing most of that sort of work?

Rutter: He would have done part, but he would have been supplemented by others as well. Pablo and I, but probably other people, too, would have been involved in that part of it. This is not what you'd call today a professional business plan. Certainly the figures and the income statements and the projections, I think that would have been largely done by Ed, with some help from other local folks.

Hughes: Was the business plan adequate when you went to potential investors, when you began to set up the partnerships?

Rutter: Well, I believe that it was, in the sense that we got investment enough to get us going, and then beyond that, the next investors were J& J [Johnson & Johnson] and Martin Marietta.

Hughes: Before we get there: you mentioned Bill Green, who was at Brobeck [Phleger & Harrison], right?

Rutter: Bill Green was, yes, initially at Brobeck.

Hughes: Bill, of course, eventually joined Chiron full-time, but not till about 1990.

Rutter: For a long time we didn't have a need for a full-time attorney. But he was part of the internal group, and he and Ed became friends. But I don't think that they were friends before.

Hughes: He was brought on because of his experience in IP [intellectual property]?

Rutter: Well, he was brought on because he was a good attorney who filled our bill well and got along with all of us. Obviously, a good member of the team, but Bill was not an intellectual property attorney.

Hughes: Tell me the story of choosing Chiron's earliest consultants. There were some even before the Martin Marietta partnership, and they're there on the outline.

Rutter: Fundamentally, we chose consultants to help us in each one of the fields. We wanted to do production in yeast, for example. So we developed relationships with folks that were related to projects or technology, and obviously we

sought advice. But we didn't establish a scientific advisory board, a board of general advisors.

Hughes: Why?

Rutter: Well, we had a coherent plan, and we felt that we needed specific advice, but we didn't need general advice. My own experience on scientific advisory boards or advisory boards in general has been that they take more time than they're worth. They are great when they are colleagues and are directly involved with the programs, but not as advisors. And furthermore, as a scientist, I'm not so interested in opinions as I am in getting something done. So to have people associated with a project made more sense to me.

So in a number of areas, we then began to involve people that had scientific knowledge or specific technical knowledge that we didn't have. A main area was yeast, because we were working on protein expression in yeast. This was clearly an advantage in the case of the hepatitis vaccine. The control of expression and secretion by sex factors in yeast had been studied by a number of people, including Ira Herskowitz. So we tried to get Ira to come on board as a consultant and in fact license us that technology. At that time Ira was more on the hesitant side about business in general. Ira didn't want to commit. So we chose Jeremy Thorner at Berkeley, another person working in the same field and a friend of Ed's. Years later, Ira then began to cooperate with us, and in fact at some point we licensed his technology. But it was typical in that era that some people were delighted to participate and others not.

Hughes: So stigma against professors in business was a factor. Yes, I know you left the chairmanship and became head of HRI [The Hormone Research Institute, UCSF]. But that in itself was a response to the criticism and the fact that your activities at Chiron were escalating. Right?

Rutter: Well, I also gave Chiron shares into a foundation in support of the [UCSF biochemistry] department, a significant number.

Hughes: From the start?

Rutter: This happened when Chiron went public. But I told people that was going to happen. And, of course, besides royalties, these shares turned out to be worth a lot of money. So in some senses the department benefited. However, it was still a very controversial area, and there were people on both sides of it, but mostly antagonistic. The same great people in science had a very considerable skepticism about doing anything with business. My guess is they were worried about the corrupting influence of money and the issue of intellectual integrity. All significant issues to be sure.

Hughes: Well, you don't have to guess. It was pretty explicitly stated at the time from many sources.

Rutter: Yes, by some people. But I think other people on the sidelines were not so explicit about it. They were just reticent. There were the real activists. Then there were the people who just didn't want to be dragged into it.

[interruption]

The general policy was to get consultants that had knowledge in specific areas we were interested in. For example, we were able to secure the services of Ed Lennette, a broadly knowledgeable microbiologist, who was invaluable in helping us understand and obtain relevant pathogens, doing testing, etc. He helped indeed.

Hughes: He did testing in his own lab at the California State Department of Public Health?

Rutter: Just handling bacteria, primarily, not viruses. Ed Lennette was an expert on bacterial infections. And Sy Fogel supplemented Jeremy Thorner. He was a good yeast person.

Hughes: Where was he?

Rutter: Sy Fogel was at Berkeley. Harold Varmus was an advisor on many subjects for sure. Tremendous person, obviously. Dan Santi later came on board in relation to projects involving chemistry, particularly peptide chemistry, where he and I had some joint patents together. Eventually, he started a small start-up company, a wholly owned spin-off company called Protos, which was devoted to the use of small biological molecules, peptides, to define targets and simplify them eventually to produce them or derivatives as drugs.

Hughes: When would that have been?

Rutter: It would have been in 1984 or 1985, something like that.

Hughes: What became of Protos?

Rutter: Eventually we had to buy it back. If you want to talk about some of those issues, we can do it at some point.

Hughes: Later, yes.

Rutter: It has to do with the business, but it's a later part of the business.

Hughes: Another consultant at this time was Hyman.

Rutter: He was an expert on herpes viruses. In our attempts to focus on targets, some of which are elaborated in that 1982 business plan, we came to the conclusion

that we could deal with the herpes viruses as a set, probably for the wrong reasons. Nevertheless, none of us were expert in herpes viruses, and so we brought in Hyman.

Hughes: Why did you say, "for the wrong reasons"?

Rutter: Well, herpes is quite opposed to the simple, small, tractable viruses that we were working on. Herpes are among the biggest and most complicated of the viruses, and in being large and complicated, they are very difficult to deal with.

[Tape 6, Side A]

Hughes: But it was a Chiron project for a number of years.

Rutter: Yes, and it was a disaster, in hindsight. The real issue is whether you want to talk about these episodes. I think in the development of the vaccine business, the work on herpes simplex 2 stood out as a high-gain but high-risk problem. It's one of the reasons why many people on the outside shied away from vaccines, and inside Chiron it gave us all the shudders.

Hughes: From the start?

Rutter: No, from the end. So do you want to talk about this right now?

Hughes: I want to talk about it at some point.

Rutter: So each one of these businesses we can take apart one by one, and the herpes problem would be interesting from that standpoint. What I would like to do is to get through this general stuff as quickly as possible.

Hughes: Yes, that's fine. There's only one remaining early consultant, and that's Randy Schekman.[7]

Rutter: Randy Schekman was a person who is knowledgeable about yeast and secretion, and we were obviously interested in secretion of molecules. His laboratory developed most of the information on secretion from yeast and the secretion process. He's an extraordinarily talented scientist and was a consultant in that area. So you can see from this early list of consultants that quite a few of them, a high proportion, were in yeast. That was the production issue and the ability to use yeast as a commercial organism. The others were related to targets, viruses and bacteria.

[7] See Randy Schekman's oral history:
http://bancroft.berkeley.edu/ROHO/projects/koshland/schekman_randy.html

So with respect to operations, then, we had fundamental research going on, and then there were offshoots, the applicability in the three different areas, and each one of the areas had potentially some business partners. Our tendency in those early days was to try to form a broad partnership, instead of a single-product partnership. So in that sense we were different than the other companies as well. We wanted a partnership in diagnostics, another one in vaccines, and in therapeutics. In therapeutics it was a product-by-product partnership, as you'd expect.

Eventually the diagnostic business could have been just on hepatitis B, because that was in the public domain. The work on other viral agents, HIV [human immunodeficiency virus], for example, began to evolve in the 1982 time frame, and of course herpes was another one of those. Besides hepatitis B, we began to concentrate on hepatitis A and non-A, non-B as a big project. So the selection was in part due to the fact that we felt that there were good diagnostic applications, and particularly in screening blood, because there the evidence was beginning to accumulate that most of these agents were transmitted by blood or could be transmitted by blood. There was a specific program in blood screening, and then there was the diagnostic area totally. So we approached many of the leading companies in diagnostics for partnership, and we got nowhere with that. This is while Jack Schuler was in charge as the president of Abbott. I think the last proposal from them had us getting 3 percent of the program.

Eventually we made a fifty-fifty-deal with Ortho [Clinical Diagnostics, a subsidiary of Johnson & Johnson], a much weaker company, but they gave us what we needed. With all its good aspects, and there were lots of good people within J&J at the time, there was an unfortunate aspect. Maybe this came from [our] naïveté; maybe it would have happened anyway, in their insisting on controlling the selling despite the fact that it was a fifty-fifty deal. I don't think we understood at the time that that itself was a major control factor, and that they were essentially driving the business from that standpoint from that point on.

Hughes: Explain that a little more.

Rutter: If you control selling to customers, and therefore all the products are based on customer interest and satisfaction, the development of new products and services is obviously driven by commercial interest. So in this so-called fifty-fifty business partnership, Ortho and J&J were the heavies.

Now, that wasn't the case in vaccines. In that instance, we were lucky enough to get the interest of Ciba-Geigy and particularly Jack Nüesch, Richard Williams (a business development person), and also the chairman, Alex Krauer.

[interruption]

Rutter: We eventually were able to convince the top leaders, in particular the chairman of Ciba-Geigy, that a vaccine was the way of the future. They had explicitly eliminated vaccines from their program. But the way that this Chiron project was presented to them was that this was a new kind of vaccine which eliminated the risks. Therefore it was a totally new approach. So we gave it a new name, Biocines. In this way Dr. Krauer, the chairman, was able to embrace the project wholeheartedly, and the Ciba-Geigy group was able to embrace the concept, in particular Jack Nüesch, who's become a long-standing friend and a great supporter.

We virtually had control over the vaccine program, except there was a heavy influence by them, particularly by the overall director of research and development, Max Wilhelm, who paid a lot of attention. In the end, they were the ones who wanted to choose a single project—success or failure based on this project. And they chose herpes simplex 2. Of course, we went along with it naïvely, not really fully understanding that this is one of the toughest problems, because herpes has a tendency to quickly hide in cells so it's unavailable to the immune system. So how does the immune system manage to contain it? It has to be through T-cells and other ancillary strategies that involve transmission from cell to cell. It's an extremely difficult problem. But it was the major project after hepatitis B. Biocine Sclavo helped support modest programs in HIV on a continuing basis. These became larger, and they became more interested in them.

With the exception of that choice of herpes, why, we remained in full control of that project. And that was truly a joint venture, not a joint business. In the general period of partnerships, we had a challenging time because we had established the principle that our partnerships would be fifty-fifty. Basically, we had the technology, they had the money and the position in the marketplace, and we should work together to develop the products, with no one having power over the other. This was simply not acceptable for most companies. They wanted somebody to be in charge, namely them, even if it was 51 percent. "Why do you care [if it's] just 51 percent?" was the common query. [Our] answer was, "Fifty-fifty." So after a while people got used to that concept, and we made many fifty-fifty deals. I think we were the only ones in the industry who championed the fifty-fifty deal. Now it is quite commonplace.

This put a lot of pressure on managing the situation and accommodating and making sure that things worked. I took about half of them, and Ed took another half. Ed was a master at dealing with the personal aspects, getting people to be quite comfortable with fifty-fifty deals. I wasn't so bad doing that either. So by and large we had really good relationships for many years with our partners. It only became difficult in the later years where we began to have muscle and wanted more control over our destinies. Then things got troublesome, I'd say mostly through one person at J&J.

Hughes: Have you said enough now about early Chiron?

Rutter: Well, with respect to day-to-day operations, Ed was CEO. He was in direct control.

[Tape 6, Side B]

Rutter: Ed took responsibility for finances, keeping the books and running the facilities, establishing overall communications with the employees, and especially external issues (a crucial role once we were in the public market. Pablo [took responsibility] with running the lab. He and I maintained very close contact about details of science, and we all talked together daily. Any significant issue, we all knew about it. Each one of us had kind of our area of responsibility, but any significant action was discussed by all of us and received our general agreement. It was a small group so you could operate that way, with a division of labor, yes, but each one of us talking to the others. It was truly a trio. I particularly focused on overall strategy, both business and science, and would argue for the projects. I did a lot of negotiation myself. Ed was Mister Outside and dealt with the financial community. I rarely did. Ed also took care of all the infrastructure issues. So it was a little bit unusual, but it worked well, in fact, until we gave it up.

Hughes: Unusual in the sense that there were three of you with sort of equal say?

[interruption]

Rutter: Well, there was a kind of hierarchy, and there's no question that I was the senior person. I broke ties, if there were ever any, and there were two or three times in our history when Ed and I didn't agree. A couple of those times we took the vote to the other people.

Hughes: To the board?

Rutter: Not to the board, to the other executives.

Hughes: Do you care to say which issues?

Rutter: No. Honestly, as I said before, there were very few times. When we did have times like this, we opened it up for discussion, and it all resolved.

Okay, so after a year of progress, we already had a vaccine in development, that is, in 1982. We had a full-scale program with Merck. We had another one with Nordisk when it was an independent company before forming Novo Nordisk.

At a crucial stage, our money was running low, and so Burr, Egan, Deleage & Co, who was our only investor, was the logical source of money. The way they presented themselves initially was that if we made progress, we'd be able to get some more money, and we'd be able to get some more money at a good price as an indication of the progress we'd made. So I visited Craig Burr, the managing director of Burr, Egan, Deleage & Co, and much to my surprise, the offer was at the same price per share or something like that. I began to argue our case, but Craig essentially made a take-it-or-leave-it offer. It seemed that he really felt he was doing us a favor at that. Needless to say, I was furious myself. I thought—we all thought—we'd made a lot of progress compared to the competition in that one year. I rejected the offer on the spot, and said it was inconsistent with what we had been lead to believe when we chose Burr Egan Deleage. We later learned that this was not only a common, it was an almost universal tactic of VCs [venture capitalists]. If you run out of money, and you don't have other sources of it, don't expect your VC to come in and automatically give you money at a price reflecting the increased value. Well, that was just another reflection of our naïveté.

So we, mostly I, didn't want to take that money, and we were playing chicken. We were virtually on the verge of running out of money. I was in Washington [D.C.] for a meeting, and miraculously Martin Marietta, the aerospace company, contacted us. They were investing in biotech companies. Somehow they found out about us. Ed took the call and immediately called me. I immediately took the afternoon off and drove over into Maryland to the headquarters of Martin Marietta, to the research wing where I met Kenneth Jarmelow. He told me that Martin Marietta was interested in diversification. To me, they looked about as diversified as you could ever get. Aside from airplanes and defense, they were in aluminum, cement, dyestuffs, and now they wanted to get into agriculture, to develop a fifth leg on their stool! The question was how to get there. So Ken's plan was to essentially put out feelers, develop little companies, and then at the right point consolidate by acquisition into a viable agriculture organization of sufficient scale to be worthy of a subsidiary of Martin Marietta. After all, aerospace was a cyclical business.

They liked the plant field, agriculture broadly speaking, but they realized that the plant field was destitute of real technology, and Ken wasn't sure of his own ability to choose. So in exchange for an investment in us, the concept was that we would help him select other companies and would help technologically some of the companies he'd already invested in. One of those happened to be Native Plants, which, as the name implies, focused on interesting varieties of native plants of various sorts. So it was a company several times larger than ours, and it was actually run by Peter Meldrum, who is now the CEO.

It appeared to us to be a very diffuse way of developing a field, but of course Martin Marietta was an extraordinarily large company, which had just

survived a challenge internally on buying another company or being bought out. So the net result of this was, we had on our board Charles Lighthouser who was their chief financial officer and had gotten considerable international acclaim for the way he had managed a takeover threat, and Ken Jarmelow also came on our board. We got a substantial increase in share price from them and a significant amount of money, and with them came some money from J &J Development Company, and so we were off to the races. The next financing, as luck would have it, occurred in the public market.

Hughes: So the Marietta deal came before the IPO?

Rutter: Yes, indeed.

Hughes: What about the consortium that was associated with this deal with Marietta?

Rutter: Oh yes, I talked about the consortium.

Hughes: Chiron was to help out; that's the consortium?

Rutter: We would help out. The consortium was a number of small companies that Marietta would buy into, and we would help choose the members of that, and then, in some sense, help to manage it.

Hughes: But Chiron wasn't just one of the boys. Chiron was the one that was going to take the lead in organizing the consortium. I mean, it wasn't an equally weighted consortium.

Rutter: Yes. We were not a member of the consortium itself, except in the choosing of the members of the consortium and providing technical advice.

Hughes: Well, let's go to the IPO. The IPO was August '83. Why then?

Rutter: All of a sudden the market opened up. The experience with Martin Marietta and with Craig Burr put the fear of a collapse of financial resources into our minds. So the market opened up, and we found we could go to the public market for additional resources. We had, after all, hepatitis B vaccine in the works. We had a program with J&J on diagnostics. We had a contract with Novo Nordisk. So we could talk about products. Therefore we decided to go into the open market and become a public company.

I remember how worried the VCs were when they first met me. They wondered whether I knew how to dress, and whether I knew how to talk, and Ed gave them comfort on these counts. They somehow, right from the get-go, sensed that Ed was kind of fair. He was very sociable and had established his relationships initially. But they must have thought that I was kind of a kook from the lab that never could possibly do anything else. So it was with some surprise that they found out that I could tie a tie and wear a suit and could

follow a line of questioning. [Hughes laughs.] Then we went on road shows, which were extraordinary in themselves.

Hughes: Give me a taste of why.

Rutter: On road shows, we talked to possible investors. I remember when we were trying to get money from investors, one of the particularly revealing meetings was with a person who ran an investment fund, who, in the midst of our presentation, fell asleep. When he woke up, he mentioned that he much preferred drilling oil wells. In that case one knew at the end whether it was a success or a failure. He thought biotech was *much* more risky than drilling for oil. As a generality maybe he was right, but not in our case.

[End of interview]

Interview 3: April 17, 2005

[Tape 7, Side A]

Hughes: I'd like to hear more about the organization of Chiron, which was largely the subject last time. Chiron, I believe, is known for its tripartite structure, the three divisions that form Chiron. How early a concept was that, and where did it come from?

Rutter: It originated from thinking about the fundamental problem facing early biotechnology companies—how to get commercial value from discovery research. In Chiron's case, we initially focused on insulin, an outgrowth of our studies on changes of gene expression during differentiation of the pancreas; and infectious disease, as a result of our early studies on the development of a vaccine for hepatitis B, which was our earliest commercial success.

I knew from my earlier experience as a consultant for Abbott Laboratories that there was a significant opportunity for hepatitis B diagnostics, and recombinant DNA technology could change both the quality and quantity of reagents, and conceptually the sensitivity and specificity of the tests. Conceptually, metrics are at the basis of science and of discovery. Diagnostics, especially quantitative diagnostics, are fundamental to developing *any* preventive or therapeutic regimen. Further, in the case of blood-borne diseases, diagnostics provide the ability to detect and eliminate contaminated blood from the blood supply. This was a major source of disease transmission at that time and a significant opportunity.

Obviously, vaccines were a core strategy for prevention of disease and theoretically represented the best strategy for control of disease. However, there were significant problems in developing effective vaccines which were both broadly potent and did not themselves *cause* disease, as had been the case for polio vaccine. Recombinant DNA methodology held the promise of constructing a "mimic" of the infectious agent in the absence of a genetic system for self-replication, hence, a "safe" vaccine could potentially be created. Hopefully, a therapeutic would evolve, and the diagnostic would be critical for detection and also to monitor treatment. Thus it was an integrated approach to the containment and elimination of infectious disease or any disease that could be immunologically contained on a straightforward basis.

So the general notion was that the same research program that supported one of these activities could, to a degree, support the other two. Potentially, one would have three earning streams from a single powerful research program. Thus the cost of the research could be allocated to these three different commercial outcomes. Also, the three avenues played out at different time frames in relationship to the research. At that time, recombinant DNA

technology opened up a new research horizon and with it immense practical opportunities.

The first outcome of course would be a diagnostic test. I believed there was an important market in using recombinant methodologies to produce better diagnostic tests. Secondly, I felt at the time, obviously wrongly, that the vaccines would come more rapidly than other therapeutics. So a vaccine development would be the second commercial outcome. And the third, then, and the least predictable, was the therapeutic approach. So accordingly we set up the three divisions to reflect the three strategies.

The problems associated with developing products would of course be different in each case, but the fundamental research and understanding of the disease would support all three. Incidentally, this strategy also reflected our experience and competence at the time. However, I believe this kind of thinking is to some extent relevant today—research organizations which are directed toward solving a particular medical problem must learn the technological intricacies, the physiological symptomatology, and all the medical issues surrounding the disease or syndrome. Those who understand the fundamental scientific/medical issues at the technical level are in the best position to make contributions to a particular problem. Frequently groups don't take full advantage of the learnings and technological advances that *they* have made, either through an internal commercial program or, alternatively, by establishing partnerships in these fields. Recently this kind of thing is beginning to happen—"companion diagnostics" are being developed by cooperative relationships between diagnostic companies and therapeutic companies.

In our case, we had limited resources both in terms of the overall cost to develop and the personnel to execute these avenues ourselves. So our strategy was to establish partnerships, much as we did in carrying out basic research at UCSF, for each one of them. A large pharma organization, I felt, mistakenly, would be able to develop all of them. At first we discussed such a broad relationship with several pharma companies, but the idea turned out to be impractical, and we eventually ended up with separate programs in the different commercial areas—J&J for diagnostics, Ciba-Geigy for vaccines, and the therapeutics programs were eventually developed internally at the IP level and subsequently licensed. Chiron later established an internal program for drug development against these infectious agents, but the programs were never really powerful because of limitations in our own organization, including resources.

Hughes: Why was that?

Rutter: Again, it was a matter of resources, and also technical scope.

Hughes: Did you know that that was a direction that you might go? Was it obvious?

Rutter: Well, yes indeed. Chiron developed a modest internal program for a drug versus hepatitis C. It might have developed as a cooperative program with Ciba-Geigy. But with the formation of Novartis, cooperative programs were never established.

Hughes: At Chiron.

Rutter: Yes, at Chiron. Today, we have a significant vaccine program and of course a profitable diagnostic business based largely on blood testing.

Hughes: How clear was it to early biotech companies that small molecules should also be in the scheme? The molecules that were first worked on were very large biological molecules.

Rutter: Well, the typical drug at that time was a small molecule, so it seemed logical to many individuals in large and small companies, especially those with experience with small molecules, that that was the ultimate solution. Gradually biotechnology companies began to focus on small molecules as well, usually directed against some novel target. By blending technologies some have been very successful.

The other aspect was hubris. I felt there was real opportunity to change the game eventually in all three of those areas. For example, until a few years ago, the diagnostics business was largely focused on the instruments of the central laboratory. There were few proprietary products. The business was built around big machines, devices which could handle large numbers of diagnostic tests in a progressively more automated form. The big companies that were involved in the development of these “Big Iron Instruments,” as I call them, were Abbott Laboratories, Roche, Bayer, J&J, Hitachi, and several other Japanese companies, and a number of other companies that have since gotten out of the game, like Hoechst. All were competing to build bigger and better instruments.

Ciba-Geigy itself had made a rather large commitment to the diagnostic business. They had been developing sophisticated central lab instruments and had a battery of tests, none of them proprietary. Eventually Chiron acquired this business in the Ciba/Chiron transaction (1986). I believed that discovery and the development of proprietary reagents presented an opportunistic shift in commercial strategy, putting more emphasis on the test itself and the components of the test, as opposed to the machine which handled it. Of course one had to have both, but the proprietary test was the factor that differentiated, both from the scientific and business perspective.

Hughes: What was your rationale?

Rutter: After all, the fundamental reason for developing the tests in the first place was their relevance to the needs of the medical community. For example, in the

case of HCV [hepatitis C virus], it was a matter of providing reagents and quantitative methods which had never before existed. In the case of HIV, initially scientists were using wild-type HIV in a cell-based test, and then progressively semi-purified forms were employed in one way or another in cell-based semi-quantitative assays. In both cases, the discovery of the causative agent—the virus—allowed the viral proteins to be produced and eventually the nucleic acid to be produced—all specific reagents that could be used in developing quantitative tests. So looking forward, new discoveries would lead to new metrics, to new diagnostics, and the proprietary diagnostics could perhaps be employed on any instrument. Why not? The novelty and hence the value was truly in the reagents and the discovery of them.

So that was the main idea behind the diagnostics business, and over time it turned out to be valid. That is to say, Chiron's proprietary position on both HIV and HCV enhanced the value of the companion HBV test, which was *not* proprietary, and the trio of tests that made our blood diagnostic business so strong. In fact, the strong proprietary position, on HCV particularly, transformed the diagnostic industry, because they were the most valuable single tests, and companies that didn't have them were greatly disadvantaged in the market.

Hughes: Was the previous focus on instrumentation largely because these companies didn't have the science to develop the tests?

Rutter: None of the diagnostics companies at the time had strong discovery science. They built their business around a set of standard tests that were commonly used, and they didn't really have the vision or scientific resources, that is, personnel, to broaden their focus. They relied on licensing the new information from outside. This is still usually the case since most new discoveries come from universities or research institutes. In the early days of recombinant DNA technology, though, many of those discoveries were being made in biotech companies like ours. Now, companies are discovering diagnostics based on multiple analytes that predict diseases, such as cancer or the predilection to develop diabetes.

Hughes: They had engineers who could build instruments?

Rutter: That's right. The diagnostic companies focused on building the instrument systems and had internal research scientists who developed the tests. So they had good technical knowledge about how you would develop a test, per se, but very poor ability to evolve their repertoire in relationship to new discoveries.

Hughes: Was there any other company developing diagnostics the way Chiron was?

Rutter: Not really. But all the major companies had some degree of innovation within their organization.

Hughes: In the beginning, you were a vaccine company; you had hepatitis B.

Rutter: That's right. The first product was the vaccine for hepatitis B, with Merck.

Hughes: Were diagnostics sort of a fallback? They were the way you hoped to bring in money to do vaccines and therapeutics?

Rutter: No, not at all. I felt there was a real business in diagnostics, and it turned out to be the case. The diagnostics business at Chiron for many years was more profitable than the vaccine business, based both on the inherent profitability in the business and especial on the return on investment. It takes relatively less money to develop a diagnostic test than a vaccine or therapeutic and, further, the risks are much lower and the timelines are shorter. Finally, the systems for readout, the instruments, can be used for many tests.

We sold part of the diagnostic business to Bayer for one and a half billion dollars and kept the most lucrative part of the business, the blood-testing business, along with the royalty stream from our proprietary tests, which was 2-300 million dollars per year. It was and is a very fine business. In retrospect, the return on investment in our diagnostic business may be one of the best in the pharma/biotech industry. Furthermore, diagnostics have a large and perhaps unappreciated impact on healthcare costs and human suffering. For example, the elimination of contaminated blood prevents the spread of disease via blood transfusion and through personal contact from individuals who are unaware of being infected. So diagnostics had what I thought were the ingredients of real success—it solved a fundamental problem in healthcare and at the same time did it in an elegant and profitable way.

Hughes: Wasn't the mindset of a lot of people in the early industry that the real way to make money was through therapeutics?

Rutter: You're right. Certainly that was the case and still is, though the thinking is changing. We were one of the few, the only major biotech company at the time, that took this other alternative, and, even that avenue was *not* easy. It turned out to be a struggle because the industry was not used to proprietary tests, and we had to fight to protect our discoveries and our technology. It took at least ten years of legal battles to protect our intellectual property, especially on hepatitis C. We had to exclude other companies from copying our tests. They initially reacted as if the information and reagents and methods were in the public domain. Further and importantly, the financial markets did not value the DX business highly. There were few analysts that followed diagnostics. Nevertheless, diagnostics turned out to be a profitable business and a real contribution to healthcare, but it was undervalued by the market.

This situation is changing today. Several diagnostic businesses financed by the venture capital community, especially by Brook Byers and Kleiner Perkins, have turned out to be profitable, and their value relative to

therapeutics is being realized by the market and also the medical community. In another dimension, the automation of histochemical tests, so important in pathology, has been an area of innovation. Ventana, developed by Jack Schuler, a former Chiron board member, and colleagues, was sold to Roche for four billion dollars.

The vaccine business, on the other hand, has been more problematic. The rather straightforward approach to developing a hepatitis B vaccine led to the belief that it would be straightforward to apply similar principles to develop vaccines for other viruses or bacteria. That is, we could use recombinant methodologies to create a molecular facsimile—a homologue that contained the essential structure, the key epitopes of the infectious agent, to which neutralizing antibodies could be directed. This was the basis for protective immunity. And this without the potential for causing disease ordinarily associated with the native virus.

Hughes: You created the molecular facsimile in yeast?

Rutter: A significant part of the problem in the development of the core structure that was intrinsically capable of producing the broad immunological response necessary to obtain broad protection was the biological system. Bacteria were not usually suitable for many reasons. Yeast turned out to be a good biological system to produce more complicated structures. But it was not an absolutely necessary component of the strategy. The general idea was to use recombinant DNA technologies to produce proteins which self-organized to form a three-dimensional structural homolog of the virus in such a way that the human immunological response to this structure would be sufficiently strong in breadth of antibodies produced and T-cell responses to neutralize the infectious agent. This strategy provided a mechanism for producing specific compounds of high purity and potentially high potency, and the process completely eliminated the chance for an infection from the vaccine itself.

The two vaccine strategies that had been used prior to this concept were the inactivation or killing strategy, for example, a vaccine based on a physiologically inactive, killed, infectious agent or alternatively the elimination of the pathological competence of the pathogen, in this case by repetitive culturing such that a viable but nonpathogenic organism was obtained. Of course the risk in both those strategies is the degree of inactivation or killing. How much do you really inactivate? Can one inactivate all of the infectious activity by these strategies? And how do you know when you have accomplished this? Have you also inactivated the epitopes which *must* be neutralized in order to obtain protective immunity?

The polio vaccine business of Cutter Labs illustrates this point. A batch wasn't completely inactivated, and as a result, many people who were given that vaccine contracted the disease from the vaccine. This incident led to great liabilities for the company in compensating people who contacted polio and a

general negative reaction from the public which never really abated. The lawsuits resulting from the "infectious" vaccine and the diminished market for the polio vaccine ultimately led to the demise of Cutter Labs. This example essentially led companies and people in the financial community to conclude that the vaccine business was not a viable business opportunity. It was too risky, both for the vaccine company and for the patients, frequently children, taking the vaccine.

Hughes: Including my brother.

Rutter: Oh my gosh! I am sorry to hear that, Sally.

The same problem exists for an attenuated virus vaccine. Sometimes infectious agents grown for extended periods of time under certain defined culture conditions lose the competence to cause disease but retain the ability to grow. These attenuated vaccines retain many of the overall characteristics of the pathological form but don't provoke the disease, yet potentially elicit an immunological response sufficiently broad to kill the natural infectious agent. Several vaccines of this sort—the Sabin vaccine for polio, for example—have been on the market for decades and are part of the traditional vaccine repertoire. However, without such long experience, the fundamental concern always exists, that under some instances, for example, in immunocompromised patients or in young children who have not developed mature immunological responses, the attenuated virus might cause disease. If vaccinated people contract the disease, it is difficult to prove that the vaccine did not in some way contribute to it. Hence the vaccine industry was for a long time subject to lawsuits, despite the fact that it was demonstrably reducing the risk of infections in populations. This issue was resolved by the government accepting some of the risks of the industry. Still, the complete elimination of risks would be preferable, obviously, to just attenuating them.

Hughes: Was that an idea that was easy to sell? Obviously, you sold it to Merck. But was it obvious at the time to other companies in the vaccine business that the recombinant DNA approach was a way that should be explored in vaccinology?

Rutter: Well, it became obvious after it had been done.

Hughes: Yes, but before that?

Rutter: Before that. Well, SmithKline had a program on hepatitis B, based on a similar idea.

Hughes: Were they working with yeast as well?

Rutter: They were also using yeast, unbeknownst to us. They were hot on our trail.

Hughes: Genentech also had a program.

Rutter: They did have a program on hepatitis B, similar to our own. In fact, Ben Hall, who collaborated with us at UCSF on the hepatitis B vaccine, was a consultant with them when I first contacted him. They were trying to replicate what we were doing in my UCSF lab. There was a big issue whether Ben would continue to work with Genentech or whether he would work with us on this project. We had all the clones and the strategy was straightforward we thought. But we needed a system to express the proteins, hopefully organized in a particle like the natural ones produced in infections. We tried to synthesize the relevant genes in bacteria and failed to obtain adequate levels of synthesis and eventually concluded we needed a eukaryotic cell, like yeast. For this, we needed a yeast promoter to drive the translation of the hepatitis B genes in yeast. Of course the hepatitis genes had promoters which were designed to be produced in humans.

Hughes: And you didn’t have that.

Rutter: We did not have it. We had extensive experience with yeast, but we didn't have the promoter we needed to make the yeast into a vaccine "factory".

Hughes: Ira Herskowitz at UCSF was a yeast person.

Rutter: Ira Herskowitz was a fine scientist who had a very sophisticated and pragmatic knowledge of yeast. But his research program was absolutely devoted to unraveling the mysteries of mating types, and he did have a [promoter], but it was not a typical yeast promoter that could be used for our purpose. He was studying the mating-type system in yeast.

Hughes: So the promoter didn’t work?

Rutter: It might have worked, but it didn’t work out for us. It wasn’t available to us.

Hughes: Why was that? You were in the same department.

Rutter: Ira didn't want to become involved in our program. In those early days, he was not in favor of commercial activities. Later on, it was another matter.

Hughes: So he wouldn’t give you the promoter.

Rutter: I tried to get him involved as a consultant and directly or indirectly to participate in the program. He just didn’t want to do it. It was part of the anti-commercialism issue at UCSF. There was a faction of UCSF who were opponents of any program that had direct commercial complications. They believed that such programs were corrupting and not compatible with teaching of graduate students and postdocs because patents were restricting and in many cases involved some kind of secrecy. Which to a degree was true.

However, I thought this could be managed effectively, just as one managed new science findings. Science itself was/is intensely competitive as well. In many cases, projects or certain aspects of projects are carried out quite privately until the result is ready for publication. Patenting and publication go hand in hand.

The group that held these opposing views included outstanding scientists and also thoughtful people. This group was absolutely against what I was doing and what Herb [Boyer] was doing and what others with similar programs were doing. I think they believed that an academic program should be oriented toward the elucidation of new knowledge, the elaboration of information, not the practical application of that knowledge, even if the practical application had come from the new knowledge that had been elucidated in the course of discovery.

Hughes: That attitude affected your career at UCSF.

Rutter: For sure. For sure. It resulted in controversy which to a degree changed the cohesive spirit of the department which we had worked so hard to achieve and to which I was committed. I felt it attenuated my ability to lead the department. There was no overt antagonism or reaction to the decisions I made as chairman. But the spirit was not the same as it had been. And a nonaffiliated but trusted arbiter, like Gordon Tomkins, was not there to ameliorate the situation.

Okay, now, back to vaccines. The idea that one could produce an immunologically functional mimic was the strength of the recombinant approach to hepatitis B. If the particles were self-organizing, they should be able to be produced in any cell that was competent to produce and secrete complex protein/lipid structures like viruses. Yeast was the simplest organism that had that capacity.

Hughes: Why would self-organization be recognized as non-self by the immune system?

Rutter: We had to rely on the intrinsic capacity of the molecules to organize in the natural conformation and not rely on additional genetic information from a human cell or organ, liver for example. The structure had to be sufficiently complex and unique so that it could be recognized as non-self by the immune system. Further, the molecules had to be so similar to the wild-type virus that the antibodies and other facets of the immune system would essentially react to it as if it were the wild-type virus. This means that it should be a faithful mimic of the natural viral structure, down to the atomic level, if possible.

The immunological system is organized to react against foreign structures such as viruses and other pathogens which are recognizably different from any of the myriad molecules that are present in the non-infected human. Assembly

into a unique structure or conformation that is sufficiently similar to the organism is necessary in order to produce antibodies in B-cells directed against the virus and hopefully also induce T-cell responses which essentially kill cells infected by the infectious agent. In addition, the immune system responds more abundantly to larger structures, such as a virus particle, rather than to smaller ones, such as proteins. Frequently multiple sites of interaction of the immune system are required in order to generate an effective immune response because of the many genetic variants in the intruding pathogen. Immunological containment is based on pervasive and multifaceted responses to a foreign structure.

Hughes: So back to the idea of partnering. Would you say, generalizing wildly, that you would be arguing the science of the deal and your partner would be arguing the business of it?

Rutter: Yes, in general, for sure. We knew more about science. We had little experience and knowledge of business. On the other hand, the insight we had was not always the same as our partners. I'll give you an example. Later, in the case of possible purchase of Connaught [Laboratories], the Canadian government vaccine business, by Ciba and ourselves, we agreed on a fifty-fifty deal. Ciba agreed to put up 95 percent of the money initially, and we would put up 5 percent. We'd co-own the business fifty-fifty, but then gradually we'd pay back the cash out of future earnings of the business. In that case, I was the one who argued that we should terminate the bidding to take Connaught, based on what I thought was the value of the business from a scientific and business perspective. We did terminate the bidding when we got into a bidding war with Merieux.

Hughes: Why?

Rutter: Too much money. It's a fascinating story. Just briefly, the company that bought it, Merieux, became so debt ridden, so undercapitalized, that Alain Merieux had to sell their vaccine business to Rhone-Poulenc, now Sanofi. That was a disaster, an internal disaster, for the Merieux family. BioMerieux was a family business which had been active for several generations, back to the time of Pasteur. The vaccine business was generated largely by Alain's father, Charles Merieux, who was a pioneer in vaccine development and who had achieved international acclaim for his achievements. It was a family legacy and quite disappointing that they became over-committed in that transaction. Now Alain has become a leader in the diagnostic field and the company is flourishing but they no longer have a vaccine business.

It just shows that when you have two parties, both of which have an interest in the outcome, it's not always the experienced individual who has the most cogent or relevant opinion. And vice versa, on the opposite side, I think many of the issues that are associated with technical developments have to do with a kind of prejudice from the technical end. So an open, unprejudiced mind may

be very valuable in rational decision making. I still believe that the fifty-fifty relationship is the best possible relationship between companies, and as long as I was at Chiron, we liked to do fifty-fifty deals.

Hughes: Was some of this an outcome of what had not been a fifty-fifty-relationship with Merck? Had you in a sense learned the hard way?

Rutter: Well, for sure, the deal with Merck [1981] was not a very good deal for Chiron and was an exceptional deal for Merck. It could also have been a bigger deal for Merck!

[Tape 7, Side B]

Rutter: The problem with this project in Merck was that it was not supported strongly within the vaccine division. It was supported by Roy Vagelos, who initiated the original deal, very strongly. On the other hand, Maurice Hilleman and his group had developed another non-recombinant hepatitis B vaccine and wanted to support that vaccine and get it out into the market. The internally developed vaccine was based on the accumulation of virus-like particles, the Dane particles, in hepatitis patients. These particles were noninfectious and apparently did not contain DNA/RNA. Hence they were a natural source of a non-infectious mimic. Of course there was still the issue of complete elimination of the virus or other viruses from this source. But in principle it was an innovative vaccine, even with the attendant risks. They were really proud of that vaccine, and Maurice did not believe that the recombinant method would work.

Hughes: Why?

Rutter: Because they didn't think we could mimic a natural process—the non-infectious Dane particles accumulated naturally in infected patients—despite the fact that we had virus-like particles that appeared very similar to the naturally occurring Dane particles. I can't tell you what would have happened if we had just gotten the production of a nonparticulate protein, as one might have gotten in bacteria. When we got particles that had the same general properties as the natural particles which exist in the blood of infected patients, we felt it was virtually a certainty that we would be able to show efficacy as a vaccine, and of course, that turned out to be the case.

Hughes: The Hilleman group resisted even with that evidence?

Rutter: Yes, probably because the other vaccine had been developed. They had begun to promote it in the market, and they felt that they could proceed with their vaccine, which was an internal project. Merck has always been a company that valued their internal developments and has largely excelled because of internal developments. Their lack of commitment was evidenced by the fact that they didn't really focus on commercialization of our HBV product. By

that I mean, they largely took our laboratory methods and translated them into a larger fermenter. Pablo Valenzuela from our lab spent many weeks essentially transferring the technology. I think there was very little adaptation of the methods to achieve higher yields or to anticipate the production of larger volumes. So they had a limited supply and for some years were supply-constrained, while they were putting their efforts into their big programs.

Hughes: On the other vaccines?

Rutter: Perhaps on other vaccines. But they were also in rapid development of new products which emanated from Roy's own interests, which turned out to be billion-dollar products. Still, we always thought of Merck as a company with immense resources and therefore felt that they could do anything and would do so, once they were committed to it.

Hughes: And that indeed was true? They could have supported your vaccine if they had so wished? It wasn't a resource issue?

Rutter: I believe it was, at least to some extent, a resource issue. And I believe that the company itself was so oriented toward therapeutic drugs—more immense markets from a revenue and profit standpoint. Every one of the divisions operated according to a budget, so the allocation of money to the budget depended upon the demands of the various activities in the vaccine division. They act almost as subsidiaries, so it would have taken a very significant decision. Undoubtedly they must have discussed the merits of the recombinant vaccine, I believe. It was such a radical difference from their previous practice that it wasn't adopted with enthusiasm initially within their vaccine business unit. Now, later on when the recombinant vaccine became a success, then of course all the folks at Merck claimed it as their own product from start to finish. This of course is not surprising and also has some degree of validity as well.

Hughes: I was at a gathering at which I met Mr. [Charles S.] Versaggi. He claimed that he and his company, Versaggi Biocommunications, had worked with Chiron. He claimed, and he even wrote an article in which Chiron was featured, that you apparently hired the company to bring back some of the claim to Chiron because Merck had virtually taken full credit for the hepatitis B vaccine work. That doesn't ring bells?

Rutter: It's a group of attorneys?

Hughes: No, they're public relations people, I suppose.

Rutter: Oh yes, now I remember. Yes, we were disturbed. We were disturbed at several levels. First of all, how the research went. Merck was supposed to provide infected liver from which the virus could be isolated. This turned out to be rate-limiting in a very competitive environment. Further, when the

research agreement was set up, we developed a royalty proposal which, if it worked, brought us, in my recollection, seven and a half percent royalty. Finally, they did not put significant effort into the manufacturing and ensuring the ability to produce the product and meet market demands. Taken all together, we thought we earned the royalty we had initially agreed to.

Hughes: That high? The press speculated 3 percent.

Rutter: Well, it was seven and a half percent. When it was obvious to us that the recombinant vaccine was going to work, then we had a negotiation with the business development person at Merck, whose name was Ed—I've forgotten his last name. Besides Ed Penhoet, we brought along Bill Green then working for Brobeck Phleger and Harrison, a major law firm in San Francisco, but soon to become our corporate counsel.[8] We felt the agreement was solid, but Merck's Ed started by minimizing our position. We started at seven and a half percent and the Merck attorney simply refused each of the stages from seven and a half percent downward in half percent intervals, ending up at half a percent! It was a roller coaster ride all the way down from seven and a half percent to one-half percent. I can remember how disconsolate we all were. This was over a couple of days, and at the end of this time, I believe particularly Bill Green, whom we relied upon as an attorney to help us through this, felt we had little alternative—we just had to accept the deal. I was furious. I said, "We're walking." And we did.

Hughes: You mean Bill Green said, "Take the one-half percent"?

Rutter: Fundamentally, yes. I mean, he felt we were helpless under the circumstances.

Hughes: That it was one-half percent or nothing, he felt?

Rutter: Yes, and that's the way that Ed of Merck essentially portrayed it. We finally ended up with two and a half percent. Well, that deal required Roy's intervention. According to Ed of Merck, Roy had told him to "make a deal." We were too stupid to insist on keeping our seven and a half percent. That was one of the biggest learning experiences that I had in all my commercial activities. I am very wary when it comes to making a deal. Very few people follow through on a verbal commitment and a handshake.

Hughes: The two and a half had been on a handshake?

Rutter: No, it was a formal agreement.

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[8] See the oral history with William G. Green: http://www.lib.berkeley.edu/cgi-bin/roho_disclaimer_cgi.pl?target=http://digitalassets.lib.berkeley.edu/roho/ucb/text/green_william.pdf

Hughes: Written?

Rutter: Written, you bet. Absolutely.

Hughes: Well, how could Merck get out of that agreement?

Rutter: Well, it's one thing to have a deal. It's another thing to *commit* to the signed deal. So Merck could walk away from it and say, "Okay, we won't develop the vaccine under these terms." What are we going to do then? They had developed the process internally, though we had helped. With money in the till from them, we could immediately develop the vaccine. If we took it back and had to start all over again, how do we do that? They recognized that a little resource-limited company like ours does not have many alternatives under those circumstance.

Hughes: Plus the fact at that point the only egg in Chiron's basket was the hepatitis B vaccine. If you didn't get that deal, I would think that the whole future of the company was jeopardized.

Rutter: To some extent that was true. But we were in a project to make insulin with Novo Nordisk [1982]. And we had a potential project with IGF-1 [insulin growth factor-1], later with Sumitomo Chemical Company and also with J&J.

Hughes: Had IGF-1 already happened?

Rutter: No, it hadn't happened this early; that was a couple of years later.

Hughes: My point is, right then and there in negotiating with Merck, when you were faced with having no deal or a two-and-a-half-percent royalty deal, it was sort of a no-brainer that two and a half was better than nothing, because it would seem to me that Chiron would have died right there on the spot.

Rutter: No, I don't think it would have.

Hughes: Why?

Rutter: Because the development of the vaccine was unique and spectacular at that time, and I think we wouldn't have let it languish.

Hughes: Meaning that you would—

Rutter: Well, who knows? I think we would have been able to find another partner, but perhaps not of Merck's status.

Hughes: Would you?

Rutter: Sure, we could have tried. But we didn't have the courage of our convictions, nor did we have the business experience that would have given us the confidence to insist on adherence to our deal. Unfortunately, Ed Penhoet and I were both green, and Bill Green, in this context at that time, was also inexperienced. Green was green. It's also true that Merck had every right not to further develop the vaccine if they chose to. So it was a situation in which they could play hardball with us, and they did.

The attenuation of the royalty stream and lack of acknowledgement of Chiron's fundamental contributions to it was a huge problem for me and also for Pablo. He had been directly involved in the work from the beginning, and it was really spectacular work. Of course Roy/Merck had also to deal with the University of Washington and Ben Hall's aggressive claims for rights as well. Part of the problem was the value of the promoter. We had to have it, but of course we felt it should have been a low-level licensing cost rather than a prominent aspect of the strategic asset. Parsing the two would have been difficult for Merck and was.

Hughes: But there was more than that, it seems to me. Chiron at that point was a company struggling for validation, was it not?

Rutter: For sure, it was early days. But I didn't think we were struggling. We had resources and good projects. We had taken only a modest amount of money from venture funds. I think we could have taken more, but it would have been a different Chiron. For sure the Merck deal gave us a validation and was very important to us. The point I am trying to make is that we probably could have made a better deal, and we should have. We should have played hard ball with UW/Ben and have been in control of negotiating the whole deal. We could have done that when Merck was down to half a percent. It certainly made a big impression on me and probably on all of us. It was a great learning experience.

Hughes: But the venture funds were soon to run out. Relatively soon you were going to have financial problems, hence the Martin Marietta deal (1982).

Rutter: That came somewhat later, but yes, money was and is a perpetual concern. The issue you raise, though, concerned the terms for the second round of venture funding that were proposed by Burr, Egan, Deleage & Co. Craig Burr didn't agree with the terms we had negotiated when we accepted the first round of funding from them. So we rejected them and sought funds elsewhere. Luckily, we were able to make an agreement with Martin Marietta, with only a couple of months' cash left. My point is that there's always an issue of risk, and the construction of an appropriately documented legal agreement is absolutely necessary in order to establish the concepts and terms of any partnership. We made many collaborative agreements. Over time, we learned what the weaknesses and strengths were, and each one of the agreements had

weaknesses and in some cases great weaknesses that attenuated the business in the future.

Incidentally, I believe strongly that Craig Burr's rejection of the deal we had initially struck with Jean Deleage for second-round financing at the time we chose them to be our venture partner led to Deleage leaving Burr, Egan, Deleage & Co and forming his own company, Alta Partners. Jean Deleage was exceedingly loyal to his biotech clients and was true to his word. He was a great help in building Chiron, even long after Alta realized its superb return on its investment in Chiron. Alta Partners became a leading biotechnology venture firm.

Hughes: Do you attribute those weaknesses in negotiation to your naïveté, or were these problems that almost any company would have run into, regardless of how experienced?

Rutter: It's a bit of both. Certainly we gained experience over time and became quite savvy in making deals. Bill Green, for example, became an accomplished deal attorney, and Ed Penhoet was excellent conceptually and in detail. Frankly, I think as a group we were very good, maybe on par with Genentech, which is saying something. Maybe pride on both sides kept us from doing deals together. There were several times we tried.

Any organization which is putting in the money eventually has some kind of superior position over another one which is not. Cash has always been king. It's a commercial deal, so cash is the key element of the transaction. Every one of our so-called fifty-fifty partnerships had aspects to them that were very positive and others that were not so positive, even negative for our business. Because of our unique situation in each of them, a junior partner in a fifty-fifty deal, we suffered both the good and the bad. And we learned a lot.

Briefly, in the diagnostic realm, the fifty-fifty deal we had with J&J was based on segregated functions. Although we shared the revenues fifty-fifty, J&J had the control on the commercial side, and we did the research and product development. We were a research company; they were a commercial company. We developed the IP, but they controlled the IP along with the commercialization and fundamentally controlled the business, despite the fact that we shared it fifty-fifty.

Hughes: Why would J&J control the IP?

Rutter: Well, because they controlled the commercial use of the IP. In the end, that turned out to be a tremendous detriment to us. We were manipulated one way or another, and we had no way to move. We were boxed into that deal, and still are on the immunological side. There were also ancillary agreements that

were made by J&J and Abbott, which in a sense optimized their overall commercial position, and we received no value from those deals. It wasn't really an absolutely clean co-ownership of the assets—a squeaky-clean, fifty-fifty deal. The person behind all of that, Ron Gelbman, was very shrewd in maximizing Ortho's [Ortho Diagnostic Systems, a J&J company] position with us. We went to arbitration a couple of times with J&J and lost as I recall. However, this general tactic of minimizing our role and maximizing his eventually led to his being fired.

Later when it came to forming an equity-based partnership with Chiron, J&J aggressively sought a fifty-fifty position in Chiron, and ordinarily we would have been delighted to do so. J&J was and is a great company, and we were on excellent terms with its leadership. But that poisonous relationship cultivated by Gelbman served to the disadvantage of both companies; it eliminated that possibility.

In the context of our original partnership agreement, we gave J&J an opportunity to participate in the development of quantitative nucleic acid diagnostic tests time and time and time again. We needed funding. J&J always passed on those opportunities. I believe that Ron Gelbman tacitly thought that if it worked, they could buy in on the cheap. Well, eventually it worked beautifully, and we developed commercial nucleic acid testing ourselves.

We developed the concept of viral load ourselves. That transformed the industry through the ability to quantitatively measure the level of the virus itself [in blood] via its DNA or RNA.This was a major step forward in the development not only of diagnostics but also any product which had an effect on the viral load, for example, therapeutic drugs. Thank heaven, we held onto those concepts, the IP, which resulted in major royalties and the most profitable part of the business. But still, J&J had control of the immunological component of diagnostics. Today Chiron has control of the nucleic acid business. The net result is that Chiron and J&J are not fully aligned in the business and therefore are not full and satisfied partners in that segment of the business.

In the vaccine business, we couldn't in general have had a better partner than Ciba. And part of that was due to the director of research, Jack (Jakob) Nüesch who really was passionate about the business and was a champion of it. A major contribution was also made by a business development person at Ciba-Geigy named Richard Williams, who came from McKinsey & Company, a business advisory firm. Richard Williams developed the strategic case for vaccines within Ciba-Geigy. He was a major asset to Ciba-Geigy, and he believed in us as vehicle for developing the business interests we shared. Ciba was an open, absolutely supportive, wonderful partner in most ways. But when it came to choosing the vaccines to develop, then they began to take pretty definitive and singular positions.

Jack Nüesch's boss, Max Wilhelm, director of research for the whole organization, decided that we should have one project. As we began looking at the repertoire of possible projects, we selected herpes as the one to go with, and not work on the other projects. We were more inclined to sort of play the field until we knew which ones were going to succeed. Herpes was the toughest vaccine to even think about in terms of prevention because the virus invades nerve cells and hides there and then, under certain circumstances, begins to display its pathological properties.

Hughes: And you knew that?

Rutter: We knew that. The interaction of herpes virus in various cells had been studied extensively. Further, several major vaccine companies, including Merck and SmithKline had tried to develop a vaccine and failed. There was still data which suggested that one could attenuate or eliminate that virus and therefore develop a product. But still it was so much more difficult than other vaccines which didn't use this biological tactic of eluding the immune system by hiding in cells and then creating pathology and infecting other cells.

Hughes: Do you think Ciba was biased by projections of the potential market?

Rutter: Probably that had something to do with it, but I think they were biased by ignorance. Max was a person who'd done very well in developing small-molecule drugs. Jack was more mechanistic in his outlook, and more pragmatic, and certainly more supportive of a technical analysis prior to the time that you committed. On the other hand, at the time they were providing the money, we listened to them—a major error on my part because my belief in hindsight is that had I persisted in looking at other targets we would have found a better one. We had a number of meetings with external experts to advise us which vaccines we should go forward with, among them scientific luminaries.

Hughes: Who were they?

Rutter: Harold Varmus and Don Ganem were among them.

Hughes: They pointed Chiron towards herpes?

Rutter: No, not at all. They were general advisors on science matters.

We considered a variety of vaccines. I think we were all flying blind because honestly it wasn't so apparent. After hepatitis B, everything seemed simple in our minds. The issue there, which has turned out to be the major issue going forward in the vaccine business, has been the fundamental one of biological mimicry. In hepatitis B, a single molecule or two molecules coming from the same gene comprise the basic structures which self-organize into the Dane particle. In other viruses, why, it's much more complex than that. There are

multiple proteins, multiple components, that need to self-organize or be organized. We simply didn't know the variety of structural configurations, and it was a rather simplistic assumption, aha, that all behave by the same process and that success would be straightforward. We only have to be able to produce the subunits, the molecules themselves, and these will be effective. Well, it turned out *not* to be true, just not true.

Hughes: How long did you persist with the yeast approach, because that in itself was flawed, was it not?

Rutter: No. We used *Saccharomyces*. A better yeast might have been *Pichia*. *Pichia* had been developed, interestingly, by an oil company, Phillips 66.

Hughes: Why?

Rutter: Well, Phillips had a little research program going on, as most oil companies do, and they chose to develop *Pichia pastoris*. This yeast had properties which far excelled *S. cerevisiae* in producing particles like those of the HBV virus vaccine. The *Pichia* technology was eventually licensed by an offshoot company from the Salk Institute, with which one of my old professors, Willis Avery Wood, eventually became associated. So *Pichia* became a major system to produce proteins and complicated structures. Chiron never licensed the technology; it was simply too expensive, we thought. We might have been wrong. Probably we should have purchased the company.

Hughes: So the fact that you were using yeast wasn't the problem in the herpes vaccine project?

Rutter: No, not at all. Up until now, no one has been able to produce a herpes-like structure, a subunit, in mammalian cells that engenders broad protection. Since our failed trial—must be ten years ago now—why, there have been no further trials of a herpes vaccine. But there has been a lot of technical development of herpes-based systems (vaccinia) for the production of proteins, etc. So somebody will do that eventually.

Hughes: Let me go back to the difficult negotiations with Merck.

[Tape 8, Side A]

If there had been an experienced business person on the Chiron team, could things have been different? All three of you were naïve in terms of business dealings.

Rutter: Yes, sure. If there had been an experienced person there who had more confidence and maybe negotiating skill than we ostensibly had, that individual might have gotten a better deal.

Hughes: Now, just to finish that story, bring in Versaggi and the public relations aspect of the Merck deal.

Rutter: Well, we were obviously very disturbed when the announcement simply called it the Merck vaccine, and there was no credit given whatsoever to Chiron. Now, let me tell you about the complexity which made it a little bit unclear. First of all, the original cloning was done in my lab at UCSF, and we set up an agreement with Ben Hall to use the promoter, alcohol dehydrogenase, that Ben had available. I struggled prior to that agreement. I looked all over for promoters in yeast. Plenty of people were working on yeast, and plenty of people had promoters, including, incidentally, a postdoc coming from my own lab.

Hughes: Who was that?

Rutter: Michael was a professor at Davis. He had a consulting agreement with Cetus. But as far as I knew, Cetus was not involved in yeast research at the time. So Mike could have easily given us some of his promoters. We simply could not get an agreement with him. Not a chance.

Hughes: Why was that?

Rutter: Well, I think everybody at that time was super aggressive in protecting their know-how, their proprietary position, believing they could form a company, or in some way become very wealthy. So we ended up with Ben Hall, who had been a previous colleague at Illinois years before and a personal friend of mine.

Hughes: And also at the University of Washington? Did you overlap?

Rutter: Indeed. Ben was a major factor in my moving to Washington after he moved there, and I was very appreciative to be in that environment. Washington was a wonderful place, and Ben and his family and I were good friends. Nevertheless, when it came to this kind of agreement, Ben essentially wanted to become a fifty-fifty partner in a business where he only provided what was truly a nonproprietary component. By that I mean, there were lots of other alternatives to get there; he provided the one that actually was available. So when we talked about collaborating, he came to UCSF with an attorney to negotiate a deal with the University of California, in which we split revenues down the middle on the expression of hepatitis B particles. That happened just during the time that we were forming Chiron, and all the work on the development of the vaccine occurred within Chiron. So Merck had to pay royalties to UCSF, royalties to the University of Washington, and royalties to Chiron. If you add all those up, it was something like 10 percent, something like that. By the way, I am told that the hepatitis B royalties were the largest single contributor to royalties of the University of California for many years and they are still coming! So the complexity was that Merck had to negotiate

with three parties separately. When Roy describes this in his recent book, [*Medicine, Science, and Merck*], he describes this as a terrific venture and mentions both me and Ben.

Hughes: On an equal basis?

Rutter: More or less. Of course, as far as I was concerned, that was so far from the truth. We just had to live with it in order to get it done. We didn't have an easy way to get any one of those promoters ourselves. We could have gotten them ourselves, and probably should have gotten them ourselves, but there was a race.

At that time, many of the companies were trying to do the same thing. When Genentech heard that we were trying to do it in yeast, of course they started trying to do it in yeast. We learned afterwards that there was a competitive program at SmithKline. The people at Amgen had a similar program. John Carbon was a member of the scientific advisory group at Amgen, was a yeast guy, and still a friend of mine. I'd been acquainted with John since my early days as a consultant with Abbott Labs. John was a very fine scientist, and he was a member of the scientific advisory board at Amgen and supported the Amgen program.

Then there was the yeast group at Genentech, who were strong competitors. So we had to get on with this program or else we would have lost in the competition. That's how it turned out, and why Merck had their own point of view about how the vaccine was developed.

Of course, Roy knew how the project originated since we had been involved since the cloning of the HBV virus, in part in a collaboration with Merck. The key person in the development was my long-time associate and colleague, Pablo Valenzuela, who was the leader of the team that cloned the virus, and also expressed the surface antigen in yeast, and finally was a major factor in purifying the yeast particle, the key element in the development of the vaccine. In fact, it was during the hepatitis B project that Pablo became a senior colleague, essentially a partner, and I agreed to split any royalties that were derived from the program, after allocation of royalties to others who also worked on the project.

Hughes: Yes, and Merck was supporting the work in your UCSF lab.

Rutter: They were supporting the work in our lab.

Hughes: Presumably, the relationship with Versaggi was an effort to recoup some of the credit. How did that work out?

Rutter: Not very well. We really did not continue that relationship beyond the planning stage.

Hughes: Do you remember what he tried to do?

Rutter: Essentially to present the case.

Hughes: To whom?

Rutter: To the public.

Hughes: Through what means?

Rutter: Well, they were going to publish articles, encourage third party reactions and things like that, and maybe approach Merck directly. As I remember it, he felt he could be a kind of business development/PR group who might help us get better deals and more of them. He felt we didn't promote ourselves as effectively as we could and should. For example, he felt we should emphasize the actual role we played in development of the vaccine, for example, provide a more accurate presentation of the roles of the two companies in HBV and vaccine development. But that was not to be, not to be, for sure not to be. I/we were very grateful to Roy/Merck for giving us the opportunity to develop this vaccine concept, and I was absolutely against some kind of confrontation which might have generated a little money in the best of circumstances, but at the cost of alienating many in the vaccine division and appearing too avaricious and acquisitive of acclaim as well.

Later on it became clear that SmithKline had developed a parallel path of producing the vaccine and that they had a more efficient process than we/Merck had. So that's why I say Merck really hadn't committed wholeheartedly to commercial development, because ordinarily when you have something like this, you try to get the best production system. That allows the company to sell more broadly at a profit and therefore compete more effectively in the market. SmithKline's method allowed them to produce much more vaccine so they could produce it more cheaply and capture more of the world market for this product. Merck's lofty reputation helped sell the product, but SmithKline's commitment to the vaccine at the practical level paid dividends in the market. Merck's share of the hepatitis B vaccine revenue was not what it should have been.

Furthermore, when it came to defending a proprietary position, there were claims and counterclaims and so on between SmithKline, Pierre Tiollais of the Pasteur Institute, and ourselves. One of the scientists at the Pasteur Institute, working with Pierre Tiollais, had developed a program directed toward production of hepatitis B surface antigen in mammalian cells. Sooner or later Biogen came in with strong claims on the virus itself, based on the identification of some sequences of HBV, which by implication meant they could have the sequence of the whole virus, including the surface antigen gene. We had sought and obtained the surface antigen gene. What had happened here?

Walter Gilbert, founding CEO of Biogen, and his lab at Harvard had been in competition with our lab to clone the HBV virus. It was not clear whether he wanted to make a vaccine. He/they had used a technique of expression cloning of the virus, cultivated in mice, to get a piece of the virus. We had ourselves independently located the gene encoding surface antigen which was specifically used in the vaccine. Nevertheless, they got IP claims which were deemed valid in Europe! Just having a little information on the virus gave them claims to the whole virus, without knowing anything about the surface antigen or its components! We can debate the fairness of that ruling, but that gave Biogen, especially with the capable and shrewd Jim Vincent (from Abbott) as CEO, the upper hand in winning the patent battle and then negotiating superb licensing deals with both SmithKline and Merck! Biogen obtained a much larger revenue stream from HBV than we did! This gave Biogen the financial resources to support the future development of the company in weakly productive times—another big lesson for us.

Hughes: To change the subject, if you were asked to characterize your management style, what would you say?

Rutter: Interactive, vigorous, and driving, forceful.

Hughes: Authoritarian?

Rutter: Perhaps a bit, in the end.

Hughes: So you would consult, but then make the decision on your own?

Rutter: Well, I honestly don’t think that I dismissed other people’s ideas, and frequently I enthusiastically accepted other people’s ideas. But I took the responsibility of making the decision in the end, taking into account, hopefully, all the various points of view. I was very cognizant of the competition we were in, and I don't like to lose competitions. I don't think I was directive, but I liked things to happen. Not always was it my decision, not always was it my idea going in, but when it came to making a go, no-go decision, yes, then I could make a decision. And that was my role.

Ed and Pablo and I talked over almost every significant decision. But I was kind of the final, final decision maker. They may not have agreed with all the decisions I made. For sure, they did not agree with everything I did. I also had developed my own view about how to run science organizations. I was a micro-manager, to be sure, within the science/technology area, and more generally a strategic leader when it came to business. I enjoyed strategic analysis, and I think I was pretty good at negotiating business deals:

Hughes: Which you had done first through the Department of Biochemistry and Biophysics?

Rutter: I did gain experience at UCSF in managing people and money and engendering a productive climate. However, running Chiron was quite different from running a research lab or running a university department or institute. At Chiron, the size and scope was ten to one hundred times bigger, and the financial/legal/strategic issues were immensely more complex. Proprietary issues coupled with large expenditures of money and commitments of significant numbers of personnel were involved. There were conflicting management styles that simply represented different ways of looking at outcomes, the market, and the world. Many people believe that a chief executive should focus on a single thing and then direct all the resources there and go forward, succeed or fail.

I didn't believe in betting the company on any one project. I believed in stressing the system: establishing and ensuring multiple ways to win. The tripartite strategy was an example of that. I subscribed to a concept I called "muddling through". This involved projection of a project to the end and anticipating the best ultimate solution, but also realizing there were less successful but still acceptable alternatives. I tried to describe and adhere to a process that essentially perpetuated the possibility of achieving the most desirable result from any time in the process. Thus, rather than establishing a precise and defined development plan that involved killing the project if it didn't reach the targeted goals in the specified amount of time, I was more concerned about the quality of the target, rate of progress, the people involved—could they pull it off? the competition—could we win?

The timelines to discover, develop, or enter the market were all hypothetical and varied greatly with the importance and novelty of the product, and certainly were variable with each product and the target market. This came down to not making firm decisions initially. You keep things open until you either have enough information to close them or you're forced to close them. I'd seen too many examples where actions were taken on the basis of some preconceived set of notions about project management. Research and development is not a kind of pharmaceutical algebra; it is more like a set of differential equations that never quite describe the actual situation, but rather describe various representations of them. That is why discovery coupled with strategic corporate development is so fascinating and challenging to me. It is the best game going, especially if you are accountable.

Hughes: That philosophy came true more at Chiron than in the department?

Rutter: Well, as I mentioned, commercial projects are much more complex than laboratory projects. So there are many more variables, including the financial responsibilities to investors and the ultimate responsibility for people's professional future, as well as their livelihood. Still, there are different management philosophies. Some would say: You pick a target, pick the leader, who in turn picks his/her team, provide specified resources, and allow Darwinian processes to select the winners and exclude the losers. You either

succeed or fail. It's like drilling for oil; it is either there or not, and one plays percentages. That was the view of Max Wilhelm, for example, on a target for a vaccine for Chiron. He selected herpes: it's a good target in the sense that it is an unmet medical need. Succeed or fail, and live with the consequences. Well, there were lots of times along the way that if we'd have been a little bit more critical at looking at all the data, we might have changed the calculus and attenuated the program.

Hughes: But he was too dominant a force to allow you to overrule him?

Rutter: Well, once you commit, then a company like that puts money behind it, and then it becomes a project. Then you have a budget, and you continue because you have money behind it. Otherwise they'd say, "Well, this group doesn't know how to run anything because they changed their mind."

Hughes: But how could you do it otherwise, if you are dependent on outside money? Receiving money from an outside source is a commitment, which I would think would really close down the options that Chiron had.

Rutter: No, we had an arrangement which covered all of the vaccine area. That was a fifty-fifty deal on vaccines. So the issue was how to develop a vaccine business with our technology. That's totally different than we have a program in which we have a single vaccine we're going for, herpes, and the whole thing succeeds or fails. We had managed to convince them that the new vaccine area was a great area for the future, and we had unusually strong technological competence, so we were good partners, so we wanted to build a new business.

Hughes: Now you're really talking about Biocene.

Rutter: Yes, that was it, Biocene. Biocene was more than just herpes.

[interruption]

Hughes: Being a strong supporter of UCSF, you have claimed very adamantly, in litigation and otherwise, that you wished UCSF to profit from technology transfer. How specifically did you see that happening? Putting it in extreme words, you could be accused of raiding UCSF in terms of personnel and research discoveries that had been supported through the public purse. I believe those criticisms were leveled, if not at you, certainly at people like Herb Boyer, who were in that first wave of commercializing academic research in biology.

Rutter: Well, the royalties from the university work from my lab exceeded those of any other project coming from UCSF in the last twenty-five years. Secondly, I put into a foundation equity that was to be used for the furtherance of research at UCSF.

Hughes: That was the California Genetics Institute?

Rutter: The California Foundation for BioMedical Research. And the money in there is more than $30 million and will accrue over time.

Hughes: So that still exists.

Rutter: That still exists, and it's being used. It was a major source of money for the [UCSF] Mission Bay project.

Most of the people in my laboratory were not paid by the university. They were employees. They had no tenure. Pablo, although he had a professor-in-residence title, had to get all his salary support from grants, initially from my grants. Pablo had many opportunities to go elsewhere. At the time we formed Chiron, he was being recruited to be director of research at Amgen. By the way, so could have Ed. So I don't understand those allegations. But that was typical of people in that time frame. Julie [Julius] Krevans has said many times that we were the only group that "did it right". I'm personally quite pleased with what happened to UCSF.

Hughes: One could argue that you had seen close up what had happened to Herb Boyer and heard the accusations about Genentech being run from his UCSF lab—all the very troubling things that happened around the time of the foundation of Genentech.

Rutter: Genentech in the early days did occupy a portion of Department of Biochemistry space, and with my explicit support. It wouldn't have happened if I had not agreed to it and actively supported it.

Hughes: My point is that you had seen what had happened to Herb and Genentech when things were not handled the way you eventually handled them. You may have decided: I want to form a company, but I don't want to put myself, my people, and my company through the terrible set of circumstances that Herb went through. So I'm going to draw the line very carefully between William Rutter as department chair and William Rutter as Chiron chairman, in a way that Herb, because he was the first, didn't know to do or chose to ignore. I think, personally, that he kind of naïvely went after founding a company without really knowing what he was going to get into.

Rutter: Well, that may be the case; many of us were to some degree naïve. On the other hand, Bob Swanson was very much more savvy. I think he was advised by the people at Kleiner Perkins, especially by Tom Perkins, who was Genentech executive board chairman, and advantaged by the naïveté of UCSF and my naïveté, too, because I agreed to stay out of the negotiation with the university for the remuneration to them [UC], and I should never have disassociated myself from that.

Hughes: You mean when Genentech was negotiating with UC, you had an opportunity to participate?

Rutter: Well, as the department chair, they [Boyer and his lab] were using space that I controlled. I was responsible for the space. Bob asked that I not get involved in negotiations with the university over conditions, including remuneration for the space. I agreed, under the condition that he treat UCSF "fairly". But his idea of fairness and mine were quite far apart. UCSF should have taken some equity in the company or in some other way have been adequately compensated.

Hughes: Why did you decide to stay out of it?

Rutter: Well, the argument by Bob was that this was a deal with the university and that it wasn't a deal with me. We probably had either competing or convergent interests, and I was a little ambivalent about that because sometime during that time period, we could have joined forces with Genentech. Therefore I did not want to be associated with making a deal with a company that I could at some level be associated with.

Hughes: You were asked to join, as we talked about last time.

Rutter: Well, we discussed joining Genentech, but the offer just didn't mature. We just never came to an agreement. It was their choice, not mine or Howard [Goodman]'s, to my knowledge, and frankly it was a good choice.

Hughes: Not to participate.

Rutter: A good choice by them, I thought, because Bob's personality and my personality would never have been fully complimentary, I think. I don't know that for sure. But I have a strong personality. He certainly had a strong personality. I wasn't used to compromising on important issues, saying, "Okay, let's cut a deal between us." There would have either been a stronger company or it would have been a disaster. I think Bob did a fantastic job in building Genentech, and I admired what he accomplished, but we had different views on some fundamentals. It probably would not have worked out.

Hughes: Then the Amgen opportunity came fast on the heels of the Genentech proposal. Were you, in the quiet of your study, thinking, "Why am I negotiating with these other people? Why aren't I forming my own company?"

Rutter: I told you, in the end I fundamentally didn't feel it was a core strength of mine to start a company, with all of its complexities. At the same time, I had my hands full, and I was loving the science that was going on in my lab. So I would have been very happy to have it continue that way.

[Tape 8, Side B]

Rutter: But in the end, competition ruled. Amgen simply wasn't decisive enough, and they wouldn't allocate enough money [to Amgen North]. That probably was a good idea, too, from their standpoint. I know Bill Bowes somewhat now and also Pitch [Franklin P.] Johnson and Sam Wohlstadter. All of those folks [who founded and financed Amgen] are outstanding individuals who are both flexible and wise. But they only had so much money, and they wanted to focus it in a certain way. They split off part of it on the device/diagnostic end to form what is now ABI [Applied Biosystems]. Then they were committed to Amgen, and they just didn't have enough resources to put behind my projects. They thought, probably, I should have just kept up with the program down there.

Hughes: At Amgen in Thousand Oaks [California]?

Rutter: At Amgen. Sam Wohlstadter quietly counseled me: "Why don't you build your own company? I'll back you."

Hughes: He said that at the time?

Rutter: Yes, and at the time he was on the board and therefore had fiduciary responsibility toward Amgen. I thought it was such an unethical position to take, I didn't want to have anything to do with Sam. But the issue was primarily competitive. I would have been happy if I had thought I'd have a competitive program [in my UCSF lab] with any one of those companies. That would have been fine with me. But we would also lose the race for hepatitis B, I have no doubt. So I wasn't ready to do that, and as it turned out, doing the hepatitis B project myself was one of the most exhilarating experiences of my life. I loved it.

Hughes: One last question, because I'm reading that you have had enough for today. I read, and it was interesting where I read it. It was in a letter from you to James Watson, when he asked you for money for Cold Spring Harbor, and you listed reasons why you couldn't contribute. One of them was that you were not receiving compensation from Chiron, that you were being paid strictly as a consultant. Why was the arrangement set up in that way?

Rutter: Well, because I was a university employee, and I wasn't a full-time person at Chiron. I had two jobs for the first ten years of Chiron. I joined Chiron in 1990 as an employee, or 1989, something like that. So I felt I could keep those two jobs. Remember, I gave up my department chairmanship because I thought that was a conflict. I became head of the Hormone Research Institute [at UCSF] and developed it as a research institute, which was not a conflict.

Hughes: Why?

Rutter: Well, because I had no administrative position, and I was only responsible to myself and building up the organization. There I had abundant programs which on a scientific basis stood by themselves. I was doing the best science of my life at that time. At the same time, I had enough time to handle all of the issues associated with Chiron, on the weekends, nights, and so on and so on. I worked long hours, and I could handle those two positions. But I was a consultant, and I had a consultant's salary, which was modest, and that allowed me to keep both jobs. It was fun.

Now we could finish the discussion on Chiron structure or organization.

Hughes: The three businesses, you mean?

Rutter: Yes, so we get that over. Okay, we had this tripartite program. How was it organized? Well, there's always complexity in a small company when you have three business orientations, and then you have a research base which supports all the businesses. There was a debate: do you have business organizations that are separate, with heads that essentially fend for themselves, like the diagnostic division and vaccine division at Merck? They make their own budget; they make their own profit, and so on and so on. It's allocated as part of a portfolio of component parts to the business. So it was always the question about how you organize research in these various areas and what authority does the head of the business group always have.

We essentially evolved into a structure such that a common research organization fed all three. To be honest, you burdened each of the three with the research that was occurring in the central division. The issue was who determined and controlled the programs. The company itself and the leadership of the company were always seeking good deals for the company. Until 1995, they went along the road of joint deals of some sort, where we would get large payments supporting the research, and we would have an equity position in the outcome of the research—equity, strong royalty, whatever, could happen.

So over time there was always a tension between the head of a division wanting to control the research that was relevant to that division—essentially, it was a fully integrated business—as opposed to the research always having equal position with heads of division and, in some senses, having a superior position. Because they controlled the money, they controlled essentially what they did. So we evolved a structure in which research itself was a component of a business-oriented division. By that, its responsibility was to get earnings in terms of royalties; to get some allocated fraction of the money that went into the various commercial entities. And that was possible for a long time because the Research Division always scouted for new projects and money coming in.

The research organ of the company was the strongest part of Chiron, no doubt. So it accumulated a lot of intellectual property and know-how in particular areas but was not restricted to a single program or to a single part of the company. This was very different than other companies. Still is. It supported the contention that in a research-driven organization, the director of research and the key players that they had used this strategy as a technical approach to a competitive advantage. For a long time we held a competitive advantage in the areas that we knew a lot about, and part of that was due to that structure. Even today, the royalties accruing from the Research Division are a major aspect of earnings. My guess is that in fact all the earnings of Chiron could be ascribed to royalties and the three businesses essentially break even.

Later on, after the acquisition of Ciba [1986], they broke it down into silos. Certainly when I left the company [1999], Sean [Lance] totally changed the corporate structure. The commercial entities have control over R&D and the business.

Hughes: How did that work out?

Rutter: Variably. That structure was the downfall of entrepreneurial and discovery research at Chiron. We began to look like any other big company.

Hughes: Had Lance gotten that business model from his past experience?

Rutter: Oh yes. Most of the big companies do that, and for understandable reasons. There obviously has be some specialty investigations of each of the areas of commercial interest. But I still believe that the director of research is the key person to deciding with the business entity which projects are the best and which people do this, and so on and so on. Again, it's this issue of a positive tension which exists between two parties that have the same objective in mind but have different responsibilities. So just like I like fifty-fifty deals, I also like a situation of shared responsibility where within the organization no single person has total control over decision making.

Hughes: But couldn't this also be a question of the evolution of a company? That in the beginning it made a lot of sense to have a dominant emphasis on research. But as Chiron grew, it became more a business than a heavily research-oriented organization? I think one could argue by the time that Sean Lance came in that Chiron required an organization that was more businesslike than science-friendly.

Rutter: Yes, many people think this way. If you've read the literature, we were accused of being a university-oriented company because we were working on a lot of projects, had a lot of good science going on, published a lot, and so on. My contention is that the business interests are not devalued by such a structure. In fact, they are more effectively developed by such a structure, because the heads of the business units do have responsibility for the

development of products and the commercial development of those products. In the typical classical structure, the head of the business unit tells the research director what to do and how to do it. My contention is, that is the wrong balance of power, and I see no evidence whatsoever that that structure is better today. In fact, most large organizations are first of all restricted to one general area so that their research officer does in fact sort of cover that area.

The other point is, that if the business units are large enough, if they're the billion-dollar size, and you're spending 20, 25 percent of that budget, well, then you need a separate person in charge of that area. But for a small company whose revenues are less than $500 million, it doesn't make any sense. If it's a research organization, it's got to be efficient, and one person needs to pay attention across the board to see that you get the most effective use of capital, both financial and personal.

[End of interview]

Interview 4: May 7, 2005

[Tape 9]

[Dr. Rutter did not review Interview 4. Sally Smith Hughes reviewed the transcript; her inserts are shown in brackets.]

09-00:00:00

Hughes: In January of 1982 Chiron signed a contract with Nordisk Insulin Laboratorium. Maybe the first thing to explain is what that was as opposed to Novo Nordisk.

09-00:00:24

Rutter: Nordisk was a precursor of Novo Nordisk. Nordisk and Novo were independent companies, both of which manufactured and sold insulin, and both of them were major worldwide companies in this field. They started early on after the discovery of insulin and became competitors with different focuses. By that I mean, Novo Nordisk was a more research-type company that had its own diabetes hospital and focused solely on diabetes. Now, they expanded after a while but [insulin] was their major claim to fame. Novo, on the other hand, had a division for industrial biochemical, that is, industrial enzymes and insulin, and it was a much bigger company. Later Novo merged with or acquired Nordisk and that became Novo Nordisk.

09-00:01:53

Hughes: After Chiron had the contract?

09-00:01:58

Rutter: Yes, indeed.

09-00:01:59

Hughes: What is the Insulin Laboratorium?

09-00:02:05

Rutter: Well, the name of the company is Nordisk Kompaniet, the Nordisk Company. Chiron's contract was with their laboratory division, which was focused on insulin and other things. There was a research program there, to be sure, and the people in research, though a small number, were high quality. They all knew about my work on the development of the pancreas. Fundamentally the history was that after we formed Chiron and we worked on the production of insulin using the natural precursor, we approached Eli Lilly about a contract that would have supplemented or superseded the one with Genentech. We felt that Chiron's process was more commercially feasible because the Genentech process involved the production of the two chains of insulin and then recombining those in vitro, which is not always a very efficient process. In fact, it wasn't efficient. And their process included things like the use of very toxic chemicals, like cyanogen bromide. In fact, I was told that if they expanded the program, they had to make a cyanogen bromide factory because they'd by far exceed the world's supply of plants.

09-00:04:23
Hughes: Lilly would have to?

09-00:04:23
Rutter: Lilly. So the reason for that was that Lilly had supported, contracted my [UCSF] lab and Howard Goodman's lab on cloning insulin, and we'd succeeded.

09-00:04:51
Hughes: Cloning *rat* insulin?

09-00:04:52
Rutter: Cloning rat insulin. Then subsequently my lab cloned human insulin in the same project. So essentially we had the sequence for proinsulin, which then self-folded, and then the intermediate peptide could be cleaved out, all enzymatically in a clean process and with high efficiency.

09-00:05:30
Hughes: Is that the process that Eli Lilly eventually took on?

09-00:05:36
Rutter: Yes, indeed. It's the process that everybody in the world uses today at one point or another. And we had that process at that time. We had serious discussions with Lilly about that project and an IGF1 project, insulin-like growth factor one, which we'd also cloned in my lab. None of them went anyplace. Eventually the people from Nordisk came to see us and proposed that we work together in some way. We finally ended up doing a project on insulin with them, and that led to this insulin production process, which I believe was the major reason for Novo to acquire Nordisk. By the way, the negotiation for the value in that process was not very successful with us; but was a very nice relationship with this group of people. But I think we only got modest rewards for it.

09-00:07:24
Hughes: Was that because of your relative naïveté?

09-00:07:29
Rutter: Well, first of all, we had no place to go. Well, we thought we had no place to go besides Nordisk. Not quite clear that was the case.

09-00:07:39
Hughes: One step in this story is that in August 1978 Lilly signed a contract with Genentech.

09-00:07:53
Rutter: Well, they signed a contract with Genentech. Are you asking why didn't Lilly turn around and sign the contract with us? Well, our process was better, but on the other hand we didn't know the details of the contract with Genentech. And eventually Lilly abrogated that process anyway. That is, Lilly abrogated the

contract and changed the process. So it was possible. The question only was one of efficiency of production.

09-00:08:23
Hughes: But why do you suppose that Lilly didn't bet on both horses? It had bet on both horses in the basic research phase because it was supporting both Genentech and you at UCSF. But it could have contracted with Chiron, too, couldn't it? Why not?

09-00:08:52
Rutter: Well, they could very much have done. Irving Johnson said in hindsight he was playing for who got there first. Not who got their best but who got there first. And it was Genentech who got there first. We started much later than Genentech, and Genentech got there first. So they elected to do what they elected to do.

09-00:09:27
Hughes: But do you suppose that was somewhat due to Lilly not having great understanding of this new science?

09-00:09:40
Rutter: No, I don't think that at all.

09-00:09:42
Hughes: No? So it wasn't so clear that Chiron's process was the better?

09-00:09:50
Rutter: I think it *was* clear.

09-00:09:52
Hughes: Well, then, I go back to that question of why wouldn't Eli Lilly have contracted with both groups?

09-00:10:06
Rutter: Well, I believe it was the nature of the contract with Genentech.

09-00:10:11
Hughes: That they couldn't.

09-00:10:13
Rutter: I think Genentech was paid handsomely, and I guess they didn't want royalties on top of that. But also there was the cloud over our work because of [plasmid] pBR322, the use of pBR322 in cloning. It's conceivable that Lilly didn't want to get into that. At the end we had a lawsuit and we lost with them.

Hughes: Well, I know from talking with Dr. [Irving] Johnson—not in this specific regard, I don't think it came up in our discussions, but in regard to the political debate that was going on at this time about the safety of recombinant

DNA—that he was ultra-careful in following the [NIH] guidelines [for Recombinant DNA Research].

09-00:11:40
Rutter: Well, they [Lilly] were certainly willing to support and conduct experiments outside of the U.S. where U.S. guidelines didn't restrict that recombinant DNA research]. So yes, they were careful. And maybe because of the supposed [pBR322] infraction, they decided they didn't want to do that with us. But I doubt it. That's a storm that only we weathered, to tell you the truth, and I don't believe it would have impinged on them at all. But I do believe at the same time that Axel Ullrich and Peter Seeburg went over to Genentech and took the clones. My guess is that Genentech promised the same deal that we had, and in fact with our clones but through Genentech. That's my guess. And I wouldn't be a bit surprised if *sub rosa* that's what happened. Who knows?

So anyway, we started this contract with [Lilly] and decided on the production of [insulin in] yeast. They knew about using yeast, and we used yeast and got a nice production method going, and eventually Lilly developed it. They also learned recombinant DNA technology from us. So it was a very shrewd relationship that was developed by Bruno Hansen and the other people.

09-00:13:46
Hughes: Was learning the technology from Chiron all right with you?

09-00:13:52
Rutter: Yeah. I didn't at all mind that part of it which was arranged more by Ed than I on the basis of good graces. I always have taken the view that in the corporate world if you do something for somebody else, you get some value for it. It's part of the equation. They weren't giving us anything for free. And in the end they really were very pecunious.

09-00:14:36
Hughes: In terms of royalties?

09-00:14:39
Rutter: Yes. They were arguing in this case that they could continue in the same way they were, just with a chemical modification of insulin and they would have done okay. Our [process] was less expensive, and they just wanted to pay us the difference.

09-00:15:08
Hughes: I would think they would have been getting a bit nervous about Eli Lilly and its branching out into recombinant DNA.

09-00:15:18
Rutter: They were getting nervous. At that time there was biosynthetic, too. You could take pork insulin and change it to human insulin by just changing the C-terminus.

09-00:15:30
Hughes: And did they have that technology?

09-00:15:32
Rutter: Yes. Many people had that.

09-00:15:36
Hughes: I'm wondering if Genentech didn't divide up the world and let Eli Lilly have this country.

09-00:15:45
Rutter: No.

09-00:15:40
Hughes: No?

09-00:15:48
Rutter: No. I assure that you that Eli Lilly was not dividing up the world with anybody and with neither of these companies. They were still battling. Whether there were *sub rosa* agreements because they didn't have very much success, and it took a lot to get into the U.S. market. And Eli Lilly had it cold.

09-00:16:12
Hughes: And had had a monopoly forever. From 1912 or whatever it was.

09-00:16:21
Rutter: Yes, but it's interesting. They had the market, but in the early days everybody complained about it because they were the only one in the market. Then Eli Lilly allowed other people in, and they even got a bigger market share, and no complaints. So it was just how they handled the public relations. It was based on competition, why that was way good, way cool.

09-00:16:55
Hughes: I know in Genentech's relationship with Lilly, there were benchmarks that they really had to race to meet in order to get the next allotment of cash. Was there a similar arrangement with Chiron and Nordisk?

09-00:17:16
Rutter: I don't remember, to tell you the truth. But it all worked so rapidly that it wasn't a big deal. We got all of our payments.

09-00:17:30
Hughes: You did, yes. How long did that relationship last?

09-00:17:40
Rutter: Well, until it became a commercial process. And after that we always had very good relationships with the people at Novo Nordisk. It terminated roughly at the time that they were acquired by Novo.

09-00:17:54
Hughes: And so insulin was the only thing that you did with them?

09-00:17:58
Rutter: Well, except we helped them on a couple of their other projects, but insulin was the main thing.

09-00:18:05
Hughes: With the technology?

09-00:18:07
Rutter: Yes. I think we did work on Factor 8.

09-00:18:14
Hughes: Well, that's what I was wondering. I think you did.

09-00:18:22
Rutter: I think as a matter of fact, we did do Factor 8 with them. In fact, now I'm certain we did.

09-00:18:32
Hughes: What became of that project?

09-00:18:38
Rutter: Well, we were behind Genentech and Genetic Systems. Is that the right one, on the East Coast?

09-00:19:00
Hughes: No, Genetic Institute.

09-00:19:00
Rutter: Yes, GI, Genetic Institute. We ended up, as a matter of fact, behind them on the papers. But the thing that we had done there was develop a factory mini-gene, which was more active than the natural one and was much more easily incorporated into the production process. So it turned out to be quite a good thing.

09-00:19:39
Hughes: Because the mini-gene was smaller?

09-00:19:40
Rutter: Uh-huh.

09-00:19:41
Hughes: Because the natural molecule is very large.

09-00:19:45
Rutter: It's very large and complex. There are lots of different sections there, including these kringle-like structures which undoubtedly form nodules in one sort or another. So in the end nobody used it because there were patents and so on. Only later it developed that we had a very strong position because of the mini-gene. As far as I know, nobody's used it.

09-00:20:25
Hughes: I wonder why. Does it function biologically as well?

09-00:20:33
Rutter: Oh, yes, it does.

09-00:20:38
Hughes: Because that was another Genentech coup, cloning, I believe, the entire natural gene.

09-00:20:53
Rutter: Maybe it was a coup, but I always thought that GI was right in there with them.

09-00:21:00
Hughes: No, I think Genentech in the end got there first.

09-00:21:05
Rutter: Maybe.

09-00:21:06
Hughes: Well, did that bring any revenue into Chiron or was it just a bust?

09-00:21:19
Rutter: Which? Factor 8?

09-00:21:21
Hughes: Factor 8.

09-00:21:24
Rutter: Only in the research agreement. I don't think it ever brought any commercial [revenue]. Up until now, I still have hopes that some of the Factor 8 uses will use the mini-gene.

09-00:21:45
Hughes: The next step then is Martin Marietta.

09-00:21:54
Rutter: Martin Marietta is a different kind of relationship. It was an investment relationship.

09-00:22:00
Hughes: And a consortium.

09-00:22:05
Rutter: Well, it was set-up an interesting consortium, but it was an investment relationship in which the consortium was a condition of the investment.

09-00:22:15
Hughes: And the consortium was Marietta's idea?

09-00:22:17
Rutter: Yes. Martin Marietta at the time was interested in diversification since they seemed to have a very narrow program--aerospace, aluminum, cement, and dye stuffs. [laughter]

09-00:22:50
Hughes: Why do you laugh?

09-00:22:46
Rutter: Well, if there's anything that's broad, it's something like that.

09-00:22:54
Hughes: Well, let's call their program non-biological. [laughter]

09-00:22:58
Rutter: Well, anyway, they wanted a fifth leg on their stool of all things, so they chose what else but agriculture since it was so close [said with irony]. And then in a stroke of genius, Ken Jarmelow, then director of research, decided that it wouldn't be a bad idea to have a company like ours help them in the selection process.

09-00:23:38
Hughes: Selection process of projects?

09-00:23:39
Rutter: Of the other companies in agriculture.

09-00:23:42
Hughes: But you were just a little baby company.

09-00:23:45
Rutter: Yet, but they were totally transformed by our vitality [said jokingly]. And maybe at the time it was justified since I think I've told you before we were just about ready to run out of cash.

09-00:24:07
Hughes: So you did have a bit of energy behind you.[laughter]

09-00:24:10
Rutter: And our esteemed investors, Burr and Deleage, had assured us there would be money available if we carried out our activities. And we did, positively. We were already on the way to developing a vaccine, and we had a lot of other projects, so we thought we'd made progress in spades. During the year, I visited Craig Burr, who was a senior partner in Boston, and he told me that they were willing to invest but at a lower price. I said, "What do you mean? Look at all the stuff we've done." "Yes, but the investment will *still* be at a lower price." Needless to say, it didn't go well with me. So I was doing my darndest to get money from some other source, not knowing anything about where to get money or whatever.

I was in Washington, DC. I think I was at a study section meeting, and Ed called me to tell me—maybe I was presenting at this meeting. Ed called me at any rate to tell me that Ken Jarmelow had called and wanted to talk to me. Martin Marietta headquarters were outside Baltimore but relatively easy to get there from where we were. And we went over and I gave him the story. Ken

was really fascinated by it and immediately set up to make a bid to buy some Chiron stock. We included two members on the board besides Ken. We had Charles Leithauser, who was the CFO, who made a very acclaimed refinancing of their company just at a time when there was going to be some buy-out or some kind of transaction. He had to borrow a large sum of money, something like five billion dollars overnight. This was well talked about in the financial press. So he joined that board. Neither of them was a scientist scientist. But Ken Jarmelow was obviously an experienced, thoughtful, single-minded, supportive person. We really enjoyed him. And Charles Leithauser, aside from not paying the executives anything, namely Ed and I, was also a very good finance man. So we had a step up in the board activities for sure with them. They bought Chiron stock at four or five times what we could have sold it.

09-00:28:49
Hughes: They bought a lot of Chiron stock. Twenty-two point five-six percent of current equity, according to my notes.

09-00:28:59
Rutter: Yes. I think they ended up owning 15 percent or something like that of the company. I'm not sure. But it was a minor amount. But I remember it was enough to completely change the history of the company in the sense that we had some solid financing. We had non-directed venture funds from a corporate company, which was unbelievably good at that time. And the only thing we had to do as payment was to go around with Jarmelow and help look at other companies, and we did look at other plant companies.

09-00:30:08
Hughes: I think there were three companies eventually selected for the consortium.

09-00:30:18
Rutter: Indeed, all of them. One of them was Native Plants.

09-00:30:22
Hughes: Right. And Molecular Genetics, Inc., was another one. Maybe there were only two others. I don't know.

09-00:30:33
Rutter: Molecular Genetics I think was this company in Minnesota.

09-00:30:44
Hughes: They were all plant companies.

09-00:31:04
Rutter: Yes, of course. They [Molecular Genetics] were working on the production of biomolecules in yeast and so on.

09-00:31:13
Hughes: Here's a list.

09-00:31:17
Rutter: Thanks for reminding me. [reading] Calgene, Plant Genetics, Advanced Genetic Sciences, PhytoGen. This is what we sent them?

09-00:31:40
Hughes: My impression is that it was their list, and what they hoped you and Ed would do is winnow it down to the three or so companies that you thought were the best fit. Do you think that's the way it went?

09-00:32:44
Rutter: Well, I think you're right. [tape break]

09-00:32:48
Hughes: This news release, I believe written by Chiron although it doesn't say so, puts Chiron as one of the participants in the consortium along with Molecular Genetics and Native Plants. [reading:] "We're ecstatic about the possibilities," says Dr. Franklin Pass, chief executive officer of Molecular Genetics. Peter Meldrum, chief executive officer of Native Plants, affirms, "It's a very powerful tool if used properly." I suppose meaning recombinant DNA. So it sounds as though Chiron wasn't just the instigator; it was actually supposed to be part of the producing consortium. Do you think that's accurate?

09-00:34:11
Rutter: Do I think what?

09-00:34:12
Hughes: Well, the way this release is worded it makes it sound, or my interpretation is, that Chiron was not just there to select companies; it was actually expected to participate, to collaborate with these other two companies. The consortium includes healthcare, which would have been Chiron. [reading:] "The purpose of the biotechnology consortium shall be to establish and develop major businesses based on biotechnology products related to agriculture and healthcare markets." [extraneous material deleted] I'm trying to establish if Chiron was an active scientific partner in this consortium.

09-00:35:42
Rutter: Yes, active in the sense that we did participate in the selection of Native Plants. We went to board meetings. We looked at their program overall. We got familiar with Calgene; didn't do a deal with Calgene nor Molecular Genetics. We became familiar with all of them except PhytoGen.

09-00:36:19
Hughes: A few years later, Chiron withdrew from the consortium. I think it was in 1985. I can't put my finger on the document right now. But was that just because you'd done what you were supposed to do for the consortium?

09-00:37:05
Rutter: Calgene moved toward products rapidly and, as you know, they eventually produced a couple of products, vegetables, and were acquired by Monsanto. Plant Genetics and Advanced Genetic Sciences were different.

09-00:37:49
Hughes: Do you remember why Chiron got out of the consortium? It didn't last very long. It lasted a few years, and then Chiron withdrew. Was there any particular reason for withdrawing or had you just done your bit?

09-00:38:45
Rutter: Well, we'd done our bit but, more than that, we just didn't buy into the strategy. The strategy had been for Martin Marietta to invest in several small companies and then at the end to combine them into a major larger company. Just on the face of it, you add value to the company, and then you buy it at a higher price after having added the value. So what's the return on investment? What's the strategy behind it? Just never made any sense. Besides that, all these little companies were fierce little companies. They weren't working in the same area necessarily. Native Plants was really producing native plants. In fact, they had quite a repertoire of native plants.

09-00:39:48
Hughes: Using genetic technologies?

09-00:39:50
Rutter: No, not always. Selection. They would get them from different parts of the world. Pete Meldrum, who is now head of Myriad Genetics, was the CEO of Native Plants.

09-00:40:04
Hughes: He was one of the names that was mentioned.

09-00:40:09
Rutter: And John Bedbrook was in one of these other companies. The classical guys were there in plant biotechnology. The fact was, very limited success.

09-00:40:31
Hughes: And that's why Chiron got out?

09-00:40:44
Rutter: Yeah. It wasn't our field, and we didn't think we were contributing very much, and we didn't buy into the business proposition. We had our own game plan.

09-00:40:49
Hughes: Had Chiron ever conceived of working in the field of agriculture?

09-00:40:58
Rutter: Yeah. One time we considered a project for producing higher levels of alcohol in yeast because we were a yeast company, and we thought we knew the mechanism for doing that. So we wondered if there were people who wanted us to try to work on that problem. Thank heavens we never found somebody.

09-00:41:29
Hughes: I may be wrong in this, and it may be something to do with Chiron's age, the fact that it wasn't amongst the very first companies to start using the genetic

technologies. Genentech and Amgen and maybe Genetics Institute, but I don't know much about Genetics Institute, had a *very* broad agenda in those early days. I think it was one of the problems you had with Amgen, that its agenda was too broad. Chiron, I believe, was never quite as widely spread out, even in your earliest days.

09-00:42:22
Rutter: Fundamentally, that's one of the differences I had from the rest of these companies. They were too spread out.

09-00:42:28
Hughes: So that was a deliberate strategy.

09-00:42:31
Rutter: For sure it was deliberate.

09-00:42:33
Hughes: Did Chiron's more focused program come somewhat from your frustration with Amgen?

09-00:42:43
Rutter: Well, a little bit came from that experience but a lot came from the fact that we just wanted to get our own projects done, and we didn't recruit a lot of money. We didn't, for example, take a lot of money from venture funds. We were frugal with the resources we had. We were all pretty practical guys. I don't think any of us would have wanted to have a program so broad that we couldn't possibly accomplish it. We already had a program that was too broad for us to do everything. But compared with everybody else, we looked like we were totally focused.

09-00:43:50
Hughes: Who was on your earliest scientific advisory board.

09-00:43:55
Rutter: We didn't have a scientific advisory board.

09-00:43:58
Hughes: Oh, well, maybe that was some of it.

Rutter: We later got scientific advisors. But I was from the beginning not enamored of scientific advisory boards because I had been on one at Amgen. And although I liked the guys, they fundamentally were not involved in the company. It wasn't those people who generated ideas necessarily; it was those people who generated ideas all over the map. I remember a great guy, Norman Davidson, and John Carbon—golly Moses, it was an idea a minute and just bubbling up all over, with a couple of dozen people in the company [to do the research]. Just totally impractical.

09-00:45:09
Hughes: Isn't there an element here, too, of over-expectation for the technology? [Extraneous material deleted] The difficulties were not so apparent at first.

09-00:46:36
Rutter: Well, every company was looking for projects and sponsors of projects. And those sponsors of projects had their own little pet projects. Oil companies had their projects, and they had money. The portfolio of projects was largely representative of the selling mechanism of the companies. And since it was kind of a novel thing [recombinant DNA technology] and pharma companies weren't jumping all over themselves to support programs in this area, why, a lot of the work just went to other fields.

09-00:47:30
Hughes: I just said that Chiron wasn't in the first wave of biotech startups, and I'm wondering what legal implications that had. Did you ever have problems because patent barriers had been setup in certain fields which you might have gone into.

09-00:48:10
Rutter: If we weren't in the first wave we were not very far behind it. So I hardly think we were in the second wave. Some of the fundamental earlier technology, which was grabbed by— There was a technology grab by Genentech.

09-00:48:32
Hughes: The Riggs-Itakura patents?

09-00:48:37
Rutter: The Riggs-Itakura and, yeah, the general cloning patents and so on and so on that gave Genentech an edge that other folks didn't have. Amgen had more money and they were [founded] earlier [than Chiron], but they were also encumbered by this huge program and were ineffectual in the early years. Biogen, yes, it started, and they had a nice program. GI was there, started more or less at the same time. They had gotten just enough ahead of us on a couple of projects. But we weren't ruled out on any project that I knew of.

09-00:49:36
Hughes: So it wasn't a problem early on.

09-00:49:37
Rutter: Well, it was a problem because any lead and any amount of money gave resources. Those companies had more.

Hughes: By the time Chiron was founded [1981], Tom Kiley, who wasn't a Genentech employee until 1980, but was involved in all Genentech's early contracts—

09-00:50:26
Rutter: Tom Kiley was, as I told you before, was the most effective patent attorney of any company and was in many respects a major source of value for Genentech.

09-00:50:46
Hughes: Yes, definitely. Bill Green had to get up to speed quickly because the legal field was already populated with Tom Kiley's?

09-00:51:09
Rutter: Bill Green was not a patent attorney. He's a corporate attorney.

09-00:51:20
Hughes: Who did you use?

09-00:51:24
Rutter: We used commercial. Tom Ciotti—Ciotti & Murashige.

09-00:51:35
Hughes: And how familiar were they with biotech?

09-00:51:39
Rutter: Well, they were early on and they worked with us. We worked with several firms, but we finally got a member of their group, [Robert P.] Blackburn, who's just now left the company [Chiron] after these many years and is a fabulous guy. But that was some years later.

09-00:52:02
Hughes: So what I'm trying to get at is, Chiron wasn't hindered by an intellectual property attorney or patent attorney having to get up to speed in the intricacies of biotech law?

09-00:52:23
Rutter: Oh, yes, for sure. I think everybody was hindered. All the firms, from Pennie & Edmonds, which was kind of acclaimed as one of the big players, they were all trying to make waves, but there were no big roadblocks fundamentally.

09-00:53:16
Hughes: Can you talk a little about patent strategy in a very general sense? For example, Herb Boyer at Genentech said, "Our scientists have to be allowed to publish," and Swanson said, "They can't do that unless we apply for patents first." That's where Kiley came in and wrote patent applications very quickly, and then they published. What was Chiron doing in that regard?

09-00:53:56
Rutter: We didn't know exactly how they did it but that's exactly how we did it. We published. We're among the most published companies for sure in that timeframe. And in terms of citations we were among the top in the citation index. We had a quick publication policy, as far as I know. The only thing that's happened is it's slowed down now in both companies.

09-00:54:32
Hughes: In later years?

09-00:54:35
Rutter: Yes.

09-00:54:36
Hughes: Just because the field was—?

09-00:54:40
Rutter: Well, depends on the attitude of the people in it. But in general people publish. They don't hold back papers for years, like was sometimes the case for pharmaceutical companies. We had the view inside the company that not only were people encouraged to publish, they *had* to publish if they were going to stay in our research organization.

09-00:55:15
Hughes: That was part?

09-00:55:20
Rutter: Absolutely. We were competitive in many different areas, and this was a hot area for publishing. We expected to publish papers and have them acclaimed as well. It added value, and it added value in the marketplace at that time, too. So it was absolutely a strategy.

09-00:55:49
Hughes: Were manuscripts reviewed by the legal department before being sent off to the publisher?

09-00:55:58
Rutter: I'm sure they were cursorily reviewed. I think I reviewed every one of them and probably so did Pablo and probably so did Ed. I don't know. But certainly I did.

09-00:56:15
Hughes: Looking for what?

09-00:56:21
Rutter: Like all the papers in my [UCSF] lab: I always managed to work on the last draft and probably the first one, too.

09-00:56:33
Hughes: Rewriting. [laughter]

09-00:56:36
Rutter: Frequently.

09-00:56:37
Hughes: I know something about that.

09-00:56:41
Rutter: I liked a clear writing style and non-ambiguous papers.

09-00:56:53
Hughes: So was it that you were more concerned about than letting out secrets?

09-00:57:03
Rutter: As far as I can remember, I never sort of inked out a section because I thought we didn't want to talk about it. I wanted to put it out there, and I wanted to get it in patents. Probably we might have been naive about some of those things, but nevertheless that's how we did it.

09-00:57:26
Hughes: That policy extended to presentations and meetings?

09-00:57:33
Rutter: Yeah. If anything, I erred on the side of telling people more than perhaps I should. I've always had the view that telling what's going on doesn't provide a disadvantage. Quite frequently it's an advantage. [phone ringing]

[End of Interview]

Interview 5: July 16, 2005

[Tape 10, Side A]

Hughes: We have talked about the earlier history of the diagnostic business, and now we're continuing that theme.

Rutter: You'll recall the diagnostic strategy was that the same research that supported prevention or vaccines and even therapeutics could be used to provide a proprietary approach to diagnostics and might provide a competitive advantage. Because our early targets were hepatitis B, for which a diagnostic business was already established by Abbott, and HIV, for which there was an egregious need, and later HCV [hepatitis C virus], which was also a tremendous and completely unknown need, we'd evolved a strategy for first developing a joint business in which we would provide the technology and the partner would provide the marketing and general support. In the very early days we had looked for an appropriate partner. About the same time that we were negotiating with Ciba-Geigy for vaccines, we were simultaneously looking for a partner in diagnostics. Because Ciba-Geigy had a diagnostic business, which we felt could be dramatically helped by proprietary tests, they were our favorite partner. But in actual fact they decided not to form a partnership with us.

Hughes: Do you know why that was?

Rutter: They had a fairly large diagnostic business, and we only had intellectual property, and we wanted a fifty-fifty deal or a rich deal. Bill Zadell, the CEO, nor any of the Ciba-Geigy folks, felt that the technology we brought merited that kind of a deal. They had bigger ambitions. So ultimately, after we looked at a number of other possibilities, including by the way Sclavo which had a minor diagnostic business at the time, we discussed such an arrangement with Abbott. I was pretty confident that we might be able to make an acceptable deal with them for I had been a consultant with them for about a decade. However, we were unsuccessful with them as well. Abbott was not willing to make a partnership with us but was willing to license our products at, I think it was, 3 percent royalty, a move which later Abbott lived to regret.

We were more successful with J&J's Ortho Diagnostic Systems. We established a joint business in the diagnostic field. This was probably due to the fact that J&J at that time were minor players in diagnostics but wanted to become more prominent in the business. Although our interest was establishing a full joint venture, they ended up proposing, and we accepted, a joint business in which they were clearly responsible for marketing and selling and therefore booked the top-line revenues into the company. We were therefore a technology partner. We had no control over sales but had control over the production of the diagnostic tests. We did share the profits fifty-fifty,

a situation which has always had its difficulties in the past because our interests were not always totally aligned.

Hughes: Meaning what, for example?

Rutter: Well, whenever one group controls the sales force, they in fact control the need for the repertoire of whatever diagnostics are being developed. So you may be a fifty-fifty partner, but you're really not in control of the strategy and execution of the business. J& J controlled marketing and pricing. We had a partnership executive group, but it was really the marketing group that determined how the business went.

Hughes: Meaning where the demand was?

Rutter: It was not always reflective of the demand of the market or in our view the best strategy for developing market share and profitability. It was sometimes a matter of how they decided to sell other J& J products as well. Of course at that time we thought that J&J, a huge international company, was the perfect partner for diagnostics. But the downsides to J&J is that they were so broad in the industry—having more than 15 companies—and their marketing and selling programs outside the United States had diagnostics submerged within the whole J&J business. So the strategy in external countries was a corporate J&J strategy; it wasn't a diagnostic strategy. In the United States and Europe, the diagnostic business operated more or less independently. But in Japan, for example, the business was Johnson & Johnson, and the head of Johnson & Johnson decided how much to spend on diagnostics and how to develop the diagnostics business in Japan. No doubt the compensation for the J&J executive was linked to total J&J top-line and bottom-line revenues. So the incentives were not tied to the performance of the diagnostic business. That was different from Abbott, who eventually became a market leader.

Hughes: How can a small company, as most biotech companies of course then were, deal successfully with an international market?

Rutter: Facing world markets for any small company is a challenge. Further, different international companies have different approaches to international markets. If a small company is lucky enough to have a product which everybody wants, they can control their own destiny. In a complex business like the diagnostic business, we eventually had a strong edge on one component of the business, an extremely profitable and important one, eventually having to do with the major infectious diseases of the time. But when we negotiated this deal with J&J, we didn't have hepatitis C. It became a true joint venture when we discovered hepatitis C and were able to develop a recombinant HIV from our work on HIV structure. The combination was truly powerful.

So the Chiron/J&J business and the imperious Ron Gelbman of Ortho Diagnostics, the head of J& J's diagnostic business, became progressively

more powerful in the field as we began to accumulate intellectual property. As it turned out, the original deals with Ron Gelbman of Ortho and Abbott Laboratories, with whom we established a licensing agreement, were always tricky because there were several two-way agreements between J&J and Abbott that were included in the overall agreements that did not involve Chiron and represented value to J&J and Abbott and came along as part of the deal.

Despite this, with the discovery of hepatitis C in 1989, the strength of our program became obvious, and J&J became a major player in immunodiagnostics. Prior to that, we recognized that just measuring the immunological response to infectious agents was not the best way to measure either infectivity or the status of the patient because there was a second-order phenomenon associated with a previous infection experience. So we started looking at other methods for directly measuring infectious agents, using nucleic acids.

The immediate focus of the business was on blood banking where there was an important need because of the period after infection and prior to the time individuals develop an immunological response, which in various diseases, like HIV, HCV, HPV [human papilloma virus], varies somewhere from the order of a couple of weeks to two or three months. During that period of time, the infectious agent itself, the virus, replicates explosively and achieves very high blood levels. So the individuals during this period are highly infectious, yet none of the immunological tests would work because this was the eclipse period before the immune response was generated. There was a possibility of measuring a protein component of the infectious agent—developing an antigen test. Later on J&J and we, among others, developed an antigen test. But I believed that the development of the DNA tests was crucial, not just for measuring the infectivity per se but also for developing any kind of drug or treatment where measurement of the virus concentration was the key to control. Believe it or not, in the late 1980s and nineties, the concept of viral load was foreign to clinical diagnosticians and medical people as a whole, who were the potential customers in the field. At that time the typical assay was carried out by incubating the sample to be tested with the appropriate cells that fostered the growth of the infectious agent. After replication, the agent would grow and multiply within the cells and then could be detected by some kind of cytopathology or some other indirect test of the virus itself.

So the biological assay took frequently days to a week, so the time was always long compared with the requirements for treatment. Furthermore, it could never be quantitative because there were variations in the growth rate and the concentrations of the virus in the inoculum. Of course the viruses were developing in the cells and accumulated in the medium where they could reinfect the cells. So the measureable virus accumulated according to some kind of a logarithmic factor that was idiosyncratic to the sample. So this inaccuracy or lack of quantitation that was inherent in this kind of assay

simply precluded an efficient development process for drugs relating to virus control or epidemiology or anything else like that.

Hughes: Now, was giving primacy to the viral load a Chiron strategy?

Rutter: That was absolutely a Chiron strategy. The concept of viral load was developed in our group, the head person of which was Mickey Urdea. I worked closely with Mickey on viral-load concepts. You cannot believe—I can't even believe today—how difficult the promulgation of that concept turned out to be.

Hughes: What was the opposition?

Rutter: Well, the opposition reflected a loyalty to the status quo. People had been doing the other for years, and they still use this older method in certain parts of the world. Of course, there were companies selling the old methods. Microbiologists were used to using them, and there were virtually no drug-development tests. The medical practice wasn't oriented toward treatment. There were not too many treatments available. So fundamentally we were entering an open field for both investigation and for diagnostics.

Hughes: The idea of viral load becomes absolutely critical in AIDS medicine, both for diagnosis and for therapy. Isn't it one of the central tenets of AIDS medicine today?

Rutter: Well, it's the central tenet in management of any viral disease and is the base of developing therapeutic agents but also of treating the patient with those therapeutic agents and also monitoring the status of the patient. So it took ten years from the time the concept was initiated until it was adopted universally. But it literally took at least a decade. In fact, I think we analyzed it rather more recently and concluded it took thirteen years.

Hughes: When did Chiron promulgate the concept of viral load?

Rutter: Well, it was in the late 1980s, close to 1990, that we started to develop that. And in developing this concept, it was correlated with attempts to develop a test which was inherently quantitative.

Hughes: I don't understand what drove you in that direction. Was it the need for quantification?

Rutter: Yes, it was the realization of the need for quantitation of the viral load, anticipating that that would be important in the treatment of patients and also in the development of drugs to treat those patients. So we saw the lack of quantification as the crucial roadblock in developing an approach to the control of viral diseases and also bacterial diseases and any other kind of

infectious disease, for that matter. But primarily viral diseases were the targets we focused on—HIV and hepatitis B and hepatitis C.

At that time, of course, we did not have PCR [polymerase chain reaction], because, as you'll recall, Cetus had already licensed PCR to Kodak and [Hoffmann-La] Roche. In the Chiron/Cetus transaction, Roche ended up with full rights to PCR. But PCR wasn't initially a good quantitative methodology. Later on, it turned out that it could be made to be quantitative. There are ways now to develop a quantitative procedure, and it's a competitive technology today and widely used. But at that time, it was difficult to make quantitative because the products themselves were substrates for the PCR reaction, and so there was a geometric relationship between the concentration and the final assay. So it was initially a better yes/no test than it was a quantitative test.

Hughes: Were you, Chiron, looking at it as a possible technology to incorporate in—

Rutter: We looked at everything at the time, and aside from the fact that we didn't own PCR, we didn't think it was the optimal good test. So the issue was, could we develop a quantitative test which provided a more straightforward result. So under the leadership of Mickey Urdea, we initiated a program on amplification of the signal, rather than amplification of the target (PCR). The use of branched DNA structures became progressively more sensitive and elegant as time went on.

Mickey started essentially with the concept that using the established principles of base pairing, one could construct a branched DNA structure comprised of a portion of DNA that would bind to target and hence provide the specificity. [It] attached to other branches that were in turn attached to chemiluminescent signals, ultimately providing a kind of Christmas-tree structure such that there is great amplification of the chemoluminescent signal from a single binding site. Further, one could employ multiple binding sites, depending on the DNA structure to be measured, to further enhance the signal and enhance the sensitivity of the assay. This was a totally different approach from PCR, which was based on amplification of the target. In the end, it was truly an elegant method in which tricks of hybridization were used, such that signal-to-noise was amplified in an exquisite way, and the practical sensitivity rivaled PCR.

Hughes: In a quantifiable way?

Rutter: In a quantifiable way, such that the signal was amplified and the noise was essentially eliminated. So it certainly became the most elegant and quantitative way of measuring viral concentration.

During all of these development years, we approached J&J because we needed funds for development of the tests, and we were partners in the diagnostic business. But J&J either refused outright or proposed such a weak financial

position with respect to the technology that it was unacceptable to us. So we struggled on using our own resources.

Hughes: J&J didn't really appreciate branched DNA?

Rutter: They did not, at least not enough to help support the development.

Hughes: And why?

Rutter: They didn't appreciate the strength of the concepts nor the strength of the methodology. I think they were more tuned to the problems associated with development of the viral load concept, the uptake by patients, and also, obviously, the troubles with developing a test like that.

Hughes: Where did PCR enter their thinking?

Rutter: Well, they were always willing to try to license PCR, but of course Roche didn't want to license it. They were looking at different methodologies and, typical of a company like that, had little sophistication in the field. As may be typical of partners in general, they underestimated our competence and will to succeed in this area. Eventually they ended up with no position whatsoever.

Hughes: But weren't people looking at PCR as more powerful? Or perhaps the question is, when did people begin to look at PCR as *the* technology, eclipsing branched DNA?

Rutter: The PCR methodology began to be used against viral load only after we established the concepts, and then because of the sensitivity of the system at that time, and because PCR was used in a semi-quantitative way everywhere in the world, they began to move toward quantitation. They eventually became quite powerful competitors. The branched DNA methodology came into its own only in the late nineties when its elegance began to show itself. Maybe I will elaborate this later when I discuss the acquisition of our diagnostic business by Bayer, because after Bayer bought the business, branched DNA became more broadly recognized and a favored method for tests of this sort for some period of time. The advantages, aside from the fact of signal application, is it soon became as sensitive as PCR—well not soon, but over time it became sensitive, and one didn't require isolation and purification of the sample. So the tests were much simpler, and the whole experimental system for measurement was very straightforward. So today branched DNA's a significant business. But it took fifteen years or more to develop, with the concept being driven by our company first, with selling the concept of viral load and our approach to it. Gradually it began to pick up steam in certain sophisticated labs, and then the other tests began to have their own approaches to quantitation, and today there are two or three different methodologies which can be used.

Eventually, the problems of this test began to be recognized. It took a lot of quality-control effort and cost to qualify the various components of the assay and the resultant cost increases. Ultimately, that was the factor that caused its demise in the diagnostic-tolerated—

[Tape 10, Side B]]

Rutter: --quantitative measurement of viral load. The signal amplification method really enhanced the diagnostic business within Chiron and elsewhere. It was broadly recognized as a purely Chiron contribution, and therefore it was the beginning of a serious commitment to the business. Not only was it then based on a proprietary position on the reagents—HIV and HCV particularly—but on a technology which essentially was revolutionizing the field.

Hughes: Was that somewhat a surprise? The way I've seen Chiron history is, it was a vaccine company in origin and concept in those early days.

Rutter: No.

Hughes: Diagnostics was always a part of the business plan?

Rutter: Absolutely, from the very beginning. And that was unique because of those two components. There were other companies focused on immunodiagnostics, but they were not focused necessarily on proprietary diagnostics, especially the crucial ones associated with blood banking, the big-volume tests. There were others that were focused on, for example, cancer tests and so on, very modest businesses that could never support the development of an instrument and so on.

Hughes: What about the concept that was adopted by Genentech, that diagnostics were a quicker way to the money than therapeutics, but that the real money in the end was in therapeutics?

Rutter: Well, that was a concept that was endemic in the industry, and of course if you're going for the real money, it was the natural way to go. But history has shown that if you make a contribution to diagnostics and if you have a proprietary position in diagnostics, it can be very profitable indeed. I think the profitability of the diagnostic business that we have demonstrates the point. Today it's a billion-dollar business.

Furthermore, the magnitude of the effect on public health may be even greater than the volume of the business. It's of course accepted that usually the metrics which a company uses are usually developed by another company. But it's also useful to have the diagnostics being developed in complement to a therapeutic program. Whether it was hepatitis B vaccine or whether it was work on hepatitis C vaccine or whatever, the availability of the diagnostics in

the same system and developed contemporaneously was extremely useful. One must have the metrics anyway.

Hughes: So that was a synergism that was delivered, or was it just coincidental?

Rutter: No, it was absolutely developed as a part of the development part of the project, as I tried to tell you. The same research that is required for both exists in the same place. So we weren't a diagnostic company at the time, but we were a company that developed diagnostics as one arm or way of creating value in dealing with infectious disease. So we saw the concept of either infectious disease or cancer or any one of the other major areas of interest for prevention and therapy to be an issue of developing a sophisticated metrics at the same time it became a precursor to the development of the therapeutic. We felt that developing the most useful metrics to a problem really was a requirement for initiating a project. If we had the best metrics, we thought we had a good chance of winning. There is no place in which it is more evident than in the development of preventive drugs or vaccines or therapeutics for infectious disease. So then we had the development of a powerful nucleic acid test, along with the immunological test.

Hughes: Meaning probes.

Rutter: Yes, of course. Then came the issue when we developed the nucleic acid test, what are we were going to do with the business of diagnostics. We could not ourselves just on the basis of the branched DNA test consider developing a new sales force and another diagnostic business. It's in that area where there are complexities of the business in the sense of manufacturing and distribution, that is, manufacturing instruments. We needed a partner, and J&J was not by this time a preferred partner. Even after we had developed the viral load tests, they were not convinced of the value and willing to put big money behind it. Furthermore, the relationships between us were not always, I would say, conducive to forming a continuing partnership.

When the Ciba-Geigy group proposed a partial acquisition in the middle 1990s, the concept was at first not at all attractive to us. But on the other hand, they were extremely good partners in the vaccine business, and we already had a fifty-fifty deal with them. We trusted their integrity as people and as a company, and they were very strategic-thinking. The director of biological research, Jakob Nüesch, who had started the program with Chiron, was a key person, but also the chairman, Alex Krauer, became convinced that our approach to vaccines could be useful in the development of products, and I think they felt we had been good partners. Our technological knowledge in general and approach was sufficiently powerful that the partnership of Ciba-Geigy with us would contribute broadly to the development of Ciba-Geigy. In addition, Richard Williams, a key business person, played a very important role.

So we were intrigued in the end and felt that sooner or later we had to have partners. It consolidated our focus and loyalties. So we attempted to propose a deal which would potentially allow us to develop as a major company independent of Ciba-Geigy but complementary to it. Anything we developed of value, they would have fifty percent of the value. Further, we hoped to establish a situation so that we would be incented to build the value of Ciba, and would work with them to establish leadership in new fields. You'll recall that transaction included the purchase of Ciba's half of the vaccine business, the purchase of their entire diagnostic business, which, as I recall, had sales of more than a half-a-billion dollars, and in addition about a billion dollars in cash and loans, which would allow us to develop our own business in these various areas.

Hughes: This became Biocine?

Rutter: No, Biocine was the designation for the vaccine portion, the fifty-fifty-deal that we had with Ciba-Geigy on vaccines. We called them Biocines because we, particularly Ciba-Geigy, wanted to distinguish recombinant DNA-based vaccine from the classical vaccines. Ciba-Geigy was not enamored of the traditional approach to vaccines, but in our case it was based on the use of recombinant-DNA methods to produce biological mimics of the natural infectious agent. It was not based on the killed or attenuated vaccines which intrinsically had the possibility to cause the disease, so it had its own intrinsic value. So that was the concept of Biocine. But then after the purchase, why, we had acquired and did continue with the use of the term Biocine because we had traditional vaccines in the acquired vaccine companies of Sclavo and also Behringwerke. So it became Chiron Vaccines. That transaction established the commercial credibility of Chiron.

We had two major businesses: a large diagnostic business, which was focused on the central lab and which could then develop and use the branched DNA technology. But [Ciba Diagnostics] had also an elegant, big machine, called the Centaur, that would be competitive with the other heavy-machinery players in the business. Unfortunately, the development of such an elegant machine takes a long time. And they also had several instruments in the Point-of-Care segment, such as blood-gas instruments that needed to be at the bedside. The business had two major facilities and was located near Boston. It had about twenty-five hundred people and became an important aspect of our business.

It became also a major responsibility because, in our opinion, Ciba Diagnostics was not run as a profit-making business. This became obvious once I was on the board of Ciba and could examine the financials. It was run as a "strategic" enterprise that was potentially profit-making but was run as an investment, not managed like one of their profit-making businesses. It wasn't required that it have the same profit margins as the other segments of their business, and it had been maintained that way for several years, so the cost

elements were simply incompatible with a profit-making business. Much good technology, many good people, but it was simply not a profitable business. They recognized that if they could bring in a proprietary set of products that that would propel their business forward, ostensibly branched DNA and the products that went with it, perhaps that was the way to do that. Their business was focused on more than branched DNA. They had a big immunological business, instruments for measurement of blood gases, and so on. They had realized, there had to be a major change in the management in the diagnostic business as well.

At about the same time, the economics of diagnostics changed. Prior to the middle 1990s, doctors would typically provide a panel of tests for their instruments, and the panel of tests had their collective value, but each test was not specifically associated with the disease they were measuring. So during the analysis of cost of medical care that occurred in that timeframe, why, all those panels were eliminated and reimbursement began focusing on single tests. This eliminated much of the profit of these very large, high-throughput machines, and therefore the profitability of the whole industry sagged.

Competition between the major companies, which were always big-iron companies, became strong, and we'd already licensed the hepatitis C tests to Ortho Diagnostics, so we couldn't use that proprietary position selectively for Ciba-Geigy instruments. Now, the DNA test was just gathering steam. It wasn't until several years later that this turned out to be so strong. So when a major revenue generator, namely the vaccine for herpes, failed in clinical trials, the revenues which might have been able to support extensive further development of a broader general financial support for the diagnostic industry, why, the company then decided that a merger would be desirable. The whole industry needed to merge. It was clear that many of the diagnostic businesses were going to fail. We had a technology-rich diagnostic business, but its commercial base was not the largest in industry, several hundred million dollars. Other companies wanted to consolidate to develop efficiencies.

So we began looking for merger partners. It was my preference at the time to do a joint venture, as we had done before, but at that time of course Ciba-Geigy was on our board, and particularly the people from Ciba felt that it was not possible to do a true joint venture with one of the major companies. So we began looking at various alternatives, and it came down to a joint venture with a smaller organization, but one which had a number of complementary approaches, like bioMerieux and Bayer. During the bidding, it became apparent that Bayer was not going to give us a fifty-fifty deal. Because their revenues were higher; we would have ended up with a minority position. And we had problems really seeing what the value of the fifty-fifty deal with bioMerieux was. The [Chiron] board didn't like a deal with a private company largely owned by a single family.

At the same time, another strategy developed within Chiron, supported heavily by Jack Schuler, who by the way was immensely valuable as a consultant and board member during the entire period. You'll recall that Jack was the head of diagnostics and eventually president of Abbott Laboratories. He was a very smart, strategic, dynamic executive who was one of the most shrewd executives in the industry. After having built the diagnostic business to a leadership position in the industry and substantially improved the performance of Abbott, Jack was fired by the CEO, Robert Schellhorn, who had typically fired his presidents, apparently in order to maintain his position and control of the business. Subsequent to firing Jack, the board of directors fired Schellhorn and asked Jack to return. Jack refused. He was off on an independent career.

As soon as I found out that Jack was available, I immediately approached him about being a consultant to Chiron. He became a major consultant and helped us develop the diagnostic business and joined our board of directors. I can't imagine a better person to have on our side. His broad experience and business sense complemented our own technical expertise and strategic inclinations. I learned an immense amount from Jack and am forever grateful to him. He had a wonderful knowledge of the market and sensed its direction, and there is no better negotiator on the planet. So when it came time for this transition at Chiron after the Ciba-Geigy transaction, we developed collectively and with his strong support the notion that the major aspect of value at Chiron was its intellectual property, not necessarily in owning all the tests and developing them.

Hughes: Explain that, please.

Rutter: Well, all the diagnostic companies wanted our intellectual property, and they all had instruments. So one of the issues within Chiron Diagnostics was we had a particular test system, and of course we benefited by the exclusive use of intellectual property. But what happened if we licensed it to everybody and then let the field decide which instruments were best? Well, we would then gather royalties. The royalties, of course, were pure profit. It eliminated the necessity of developing instruments, the cost of selling them, everything else.

Hughes: Did that strategy come from Jack Schuler?

Rutter: Well, it was certainly supported by Jack Schuler. I think it was developed cooperatively by Jack and me, but also with input from Ed Penhoet and Pablo for sure. I had earlier developed the concept of a separate business unit which was really based on intellectual property. Our royalties were a strong component of the J&J business. And as we developed intellectual property in general from both Chiron and from the acquisition of Cetus, intellectual property was a major product of our research program. So it was the profit motive for research when we didn't develop products ourselves. When one began to think of the magnitude of this going downstream, as long as we

could maintain the research, why, this became essentially the product of research and a core aspect of value. So when we then analyzed the segments of the diagnostics business in the context of profit instead of revenues, it became obvious that the greatest profit was associated with licensing other organizations to use the intellectual property in their diagnostic business in exchange for the high royalties we could command.

Now, the segment of the business that didn't fit that principle or the place where that principle was modified was in blood banking, because there we really could control the field. Our intellectual property essentially covered the field. Hepatitis B, HIV, and HCV were the big tests in that field, and second of all, there needed to be developed new test systems. Blood banking where our branched DNA and our technology were arguably the strongest was where our unique technology was focused, and it was a small enough business so that we could run it ourselves without large infrastructure costs. So when we sold the diagnostics business to Bayer Diagnostics, we kept the IP to the diagnostic tests, which they licensed for their business. This was the most profitable segment and still remains so.

Curiously, at that point, the bDNA methodology was sold to Bayer in its entirety, and we had to develop another methodology. It turned out that Mickey [Urdea] had already decided, as we looked carefully at the various alternatives, that an approach developed by GenProbe, which was also a chemical approach, had some advantages over bDNA. It was a less costly system to develop. The bDNA methodology was in trouble because we had nearly fifty reagents that we had to deal with in QA/QC [quality assurance/quality control], so it was a horrendous problem to manufacture. It only became profitable when the business became large. So you needed a large influx of capital in order to develop the volume that would support such a complex test. The GenProbe system was much simpler in the sense that the components were far fewer. It was also sensitive, and in the end, we determined it was more practical for the diagnostic business.

Hughes: Was that part of your strategy behind selling the bDNA technology?

Rutter: Well, it became a component of the strategy. Obviously, we wanted to maximize the yield from the diagnostic business, and we got an excellent price. We got one and a half billion dollars, and we kept both the intellectual property and the blood banking business which were the highly profitable parts. So fundamentally, we got an acceptable price, and we got more profit, and we kept the core high-value part of the business. The fact that we had an alternative to bDNA to develop in this partnership with GenProbe was an element in all this, for sure. So this then provided, since the late 1990s, the basis for a very profitable blood-banking business, in which we're the technological leader and, in fact, the business leader, too. This was a great example of good science and good business.

[Tape 11, Side A]]

Rutter: As far as I can tell, we've never been able to somehow come to an agreement with J&J on convergence of the two businesses. It would clearly be, at one level, an advantage to converge the two businesses into a single business, but we disagreed with J&J on the value of their approach to a system for immunological diagnostics. They developed their own instrument, and from time to time we'd had differences of opinion about the best way to evolve that business. Suffice it to say that Ron Gelbman left J&J—I think by invitation of the upper management of J&J—after the unsuccessful attempts to acquire or form a joint venture with Chiron. (J&J was a competitor of Ciba-Geigy in the acquisition of Chiron.) Because of our difficult relationship with them in diagnostics, we decided that Ciba was a much better partner. In addition, we got a much better deal from Ciba, though we didn't really carry our bidding war between the parties. We committed ourselves to Ciba on both strategic and practical grounds. However, even after the Ciba deal, we maintained the separate immune and DNA-based businesses with J&J, and luckily both have been highly profitable and a core aspect of value now. The immunodiagnostic business makes a major contribution to blood banking, and the development of an automated nucleic acid test system with GenProbe makes it the most efficient system for measuring nucleic acid tests in the blood banking environment.

Hughes: Are all these things today really the fundamental technologies of Chiron's diagnostic business? I guess what I'm really asking is, has Chiron Diagnostics moved on in any substantial way in the last decade or so?

Rutter: Not technologically. The instrument system for measuring high volumes has been developed progressively, in concert with GenProbe. So the state of the art now is measuring all three diagnostic tests in the same system, the triplex test. That makes everything easy. So the sophistication of measurement and the ease of measurement of probe tests have increased dramatically with the development of those instruments, but fundamentally the technology is the same.

Hughes: Is it the most profitable of Chiron's present businesses?

Rutter: Well, yes, for sure it is, but it depends on how you allocate costs and attribute expenses. The vaccine business has been growing. It takes a long time to develop new vaccines. Our hepatitis B vaccine was out-licensed to Merck, which in turn cross-licensed the technology with SmithKline. Those companies are the ones that have highly profitable businesses in hepatitis B. Then our own vaccine business built on Sclavo and very classical vaccines. Chiron has been attempting to develop modern vaccines for HIV, HCV, and a number of other diseases. [Biocine Sclavo] did develop a recombinant vaccine for pertussis, and are now in the process of developing one for other major

diseases, including hepatitis C and HIV. But it has taken a long time. Unfortunately, those projects have turned out to be very much more difficult than hepatitis B.

So the vaccine business has been a growing business and an increasingly profitable one. But of course the problems with the flu vaccine manufacturing in the last year or so have dramatically affected the profitability of the vaccine business. [Dr. Rutter refers to contamination in one of the facilities manufacturing Chiron's flu vaccine.]

When Sean Lance took over [Chiron] as the new CEO, he wasn't convinced that the vaccine business was or could be a profitable business, and so the vaccine business was in, let's say, an ambivalent state for several years. Eventually they committed to the vaccine business and in fact bought PowderJect. PowderJect would have been a significant source of profit provided that they could have run it technically such that they could produce the volume that was required. But that turned out not to be the case.

So I'd say that after I left and Ed left the vaccine business has gone from a core business to a questionable status in the Chiron repertoire. One doesn't know what is going to happen there, but it's still a tremendously valuable business. From a technological point of view, Chiron has contributed greatly to the technology of developing vaccines and has very interesting vaccines in development, including, I think, a very good approach to hepatitis C, although it takes a long time for them to go through the development process. For many years we were in the front rank of the HIV vaccine program and had an absolutely novel approach to meningococcus and other bacterial vaccines.

Hughes: Some of this return to vaccines as a core business was due to legislation and other initiatives in the wider society to make vaccines a less risky business?

Rutter: Well, certainly that helped. That helped support the vaccine business in general. But vaccine businesses, as you know, were developed from a public-health orientation. Each country had its own approach, and therefore each country had its own production facilities of the standard childhood vaccines and other vaccines. As a result, each country had its own process for regulatory approval which made it complex to get approvals for vaccines—much more complex than for drugs. And therefore the testing procedure became truly complex, time-bounded, and is today one of the biggest challenges to the industry.

Hughes: Do you think that was Lance's prime reason for wanting to back-burner the vaccine business?

Rutter: No. Lance told me that he believed that even if there were development of an HIV vaccine, it wouldn't be profitable. The reason for that was that it would be necessary to provide the HIV vaccine to the rest of the world.

Hughes: That's exactly what's happening, isn't it, that companies making vaccines are forced to give them at much-reduced prices to the developing world.

Rutter: Yes. On the other hand, it's also true that those various companies are making a lot of money doing it. This is not a profit-loss situation. In fact, there has been great support by the World Bank, by the various countries, for support of the worldwide vaccine program, and the vaccine initiatives worldwide have in fact supported worldwide programs. SmithKline has become immensely profitable, producing fundamental vaccines for the rest of the world.

Hughes: Even though they're at a lower price.

Rutter: Lower price, absolutely, but you can produce them at high volume. The wonderful thing about vaccines is that they lend themselves to mass production. So it's absolutely wrong to conclude that the companies that sell to the rest of the world have become unprofitable. I think hepatitis B is an example of a vaccine which is sold all over the world, and it's also a very profitable vaccine. It's a multimillion-dollar vaccine. You watch, whether it's the new papilloma vaccine which is going to be sold all over the world or a hepatitis C vaccine or a vaccine for diarrheal diseases, which are largely third-world diseases, they're all going to be very profitable. I totally disagree with the concept that you won't be able to make a profit.

Hughes: Is Chiron working on all those diseases?

Rutter: No. Chiron's program on HIV has been attenuated because they want to get others to support the development of it, and they do have support from the NIH, but it's not a leading program.

Hughes: What about hep C?

Rutter: The hepatitis C vaccine is being developed by Chiron, as far as I know as an internal program, despite long efforts, which were really due to the difficulty of manufacturing the components of the vaccine. I have heard that they have ultimately found a good way to manufacture it, but whether it will ultimately become a vaccine is an issue. I think it does not have the support of upper Chiron management, sad to say.

Hughes: This is quite a shift, is it not, in the vaccine business? Not just at Chiron but in the pharmaceutical industry in general, vaccines have had a problematic history in terms of profitability, liability, and other issues that have made them, in many cases, a less desirable business to get into.

Rutter: Yes, there are complexities in the business. But I disagree with the concept that they are intrinsically unprofitable. I think that that's a common view, and it is true if the vaccine business were simply focused on all vaccine companies doing the same thing, namely developing childhood vaccines. That is a highly

competitive field. There's no intellectual property. It's just an issue of manufacturing volume and cost. There is still room for two or three major companies, all of whom are very profitable today in different areas: Merck, Aventis, now Santofi-Aventis, and GlaxoSmithKline. And hopefully now Novartis.

Hughes: Has the new perception of profitability in the vaccine business had a repercussion in the biotech industry?

Rutter: The only way the perception has changed is because of the necessity of controlling disease and the realization that many diseases need to be much better controlled. So [there has been a] progressive understanding of prevention as a core element in disease control, both in terms of cost and in terms of the reality of outcomes. The application of the new technologies based on recombinant methods and the advances in immunological methodologies, adjuvant development and so on, have all helped. There have been several new technology-oriented vaccine companies. Unfortunately, none has achieved spectacular success as yet. You have the elements of a knowledge-based industry, and with the opening of the entire world, then diseases become a major issue for every place in the world. So it's a natural driver. It was already obvious twenty-five years ago that it was going to happen. It was only a question of when. And it was particularly evident after the fall of the Berlin Wall when it became obvious that we would eventually have a world that had interrelated currencies, exchange of markets, exchange of people, and so on.

Hughes: Yes, the global economy.

Rutter: We really then had a related social economy at the same time, in which disease is the centerpiece.

Hughes: We should bring Mother Nature in here, too, I think. Some time ago, there was the belief that infectious disease had been conquered, and then practically as soon as people began to mouth that concept, Mother Nature began to show her stuff, and we've had a series of outbreaks of infectious disease with global implications. I'm thinking of SARS [severe acute respiratory syndrome] and avian flu, etc., that underlined the need for continual development of vaccines against new diseases as well as the old.

Rutter: Well, absolutely, and as an historian, it might be interesting to focus on the change of opinions, even among scientific leaders, especially in HIV disease, from the notion that you could handle it by drugs to the notion that you couldn't handle it by drugs. You had to deal with prevention by any method possible. And the same thing is true for every endemic disease. Drugs are rarely the total answer. They're a partial answer. But also there's a tremendous development of new information about the complexity of those diseases and how to measure them, the life cycles of infectious agents and so

on. So truly, what was a black box when we started in the vaccine business is now showing some luminosity. It certainly isn't as easy as it was as first perceived, but there is real progress. In the end, there will be real control based on prevention and immunological strategies for treatment as well as prevention.

So getting back to the point: the strength of Chiron and the seminal influence that we had on both of these fields was due to the fact that we concentrated on infectious disease as a fundamental problem of humanity which was going to be controlled by new scientific developments and the evolution of understanding on a social, political, and economic basis. So it was a big idea that required real support, and one way or another we got it.

Hughes: We talked about how the model for hepatitis B vaccine was optimistically thought to be transferable—obviously with some adjustments. But you did not initially believe there would be tremendous difficulty and long time periods in developing other vaccines?

Rutter: Clearly there were two problems in the development of the vaccine industry, both of which I underestimated. The first of them had to do with the technical issues of mimicry. Hepatitis B was a piece of cake because it was a single molecule and self-organized into a structure that was already observable in the serum of patients with the disease. In other instances, the structures were much more complex, and the idea of subunit vaccines, which was thought plausible by many, just didn't work out. Both the structures and the ability of infectious agents to elude the immune system were not fully comprehended.

Hughes: Like herpes.

Rutter: Well, herpes is certainly a case in point and is different from HCV. It is a much more complicated virus, and it resides inside neurons so it is difficult to be controlled by antibodies. One needs T-cell responses, and you need to provide a structure which contains an epitope which is required for function. In order to achieve immunity, antibodies must be directed to this or several epitopes which in the aggregate provide immunological control without the possibility of escape by mutation, and they must persist indefinitely. Finding the key elements required for control has been difficult. So it becomes a multiple problem, the biological mimicry part. And the notion of subunits doing the job, which was the initial strategy that we and others participated in, the basis of our herpes trial, was that a stronger immune response against some key antigens of the virus elicited by adjuvants would do the job. Unfortunately, in this case the system provoked an enhanced disease in some patients! Some of the antibodies promoted the infection. Clearly, a higher level of complexity and more sophisticated understanding and analysis is needed in such diseases. There are times when a problem is ripe for a solution, and that time was not ripe for HIV or for herpes. Today, the situation is different.

Hughes: Meaning the candidate vaccine didn't work.

Rutter: Didn't work. Subunit vaccines don't work. You have to have the three-dimensional orientation of a substantial structure that contains key epitopes. Secondly, there is an additional complexity. That is, in certain instances, antibodies can exacerbate the disease as well as prevent it.

Hughes: Which was completely unknown in the early eighties?

Rutter: It was largely, if not completely, unknown, and is only now becoming understood.

Hughes: Did that finding come out in vaccinology?

Rutter: Yes, it came out in the herpes trial. Our methodology, using the adjuvants and the components, developed a hundred times higher antibodies than the previous trial, which had been carried out by Merck. So in simple systems, it seemed very promising. It was going to work. But it turned out that there were certain subsets in which the vaccine might have enhanced the infection instead of inhibiting it. So these cases just raised the issue of how do you tailor the vaccine so you get around that?

Hughes: Subsets of people?

Rutter: Subsets of people, mostly women. So fundamentally it raised another problem, which had to be dealt with in certain instances and required a new technical approach.

Hughes: Which Chiron began to work on, or did you drop the herpes vaccine at that point?

Rutter: We dropped it, despite the fact that a number of our academic colleagues felt that there was an approach to the vaccine which might have worked. But at that time the risk seemed too great, and we had other target diseases, like HIV and HCV, to target. Herpes is a peculiarly difficult infection to contain because the infectious agent persists in nerve cells, and so you have to protect the individual before it becomes sequestered from the immune system. Also one must kill the infected cells by T-cell-mediated responses. We realized that it was a difficult problem at the start, but it was a choice made collectively with Ciba-Geigy. The head of Ciba-Geigy's research program, Max Wilhelm, was convinced that we should go for herpes, and we agreed to go forward. A very bad decision on our collective part.

Hughes: Was Chiron able to absorb the people that were working on the herpes project?

Rutter: Yes, for years, as long as there were other vaccine programs. And, for sure, we had to stop and rethink, and some of the people from those programs left. But the vaccine business itself was going strong, and many of the people that were involved in those programs are still at Chiron.

Hughes: When you count the time Chiron has spent on trying to develop AIDS and hepatitis C vaccines, it's taken a lot of money and persistence, hasn't it?

Rutter: Well, it does take money and persistence, and dedication, and if you are dedicated to a resolution of the problem over some period of time, one can get there. The beautiful thing about vaccines is when they work, they are useful for a long time, decades in fact. I think that part of the problem of the vaccine business has been that progress has been science-restricted. That is, there were knowledge gaps about the infectious agents and their interaction with the immune system. But there is also a huge external problem. It's the regulatory problem worldwide. The complexity of regulatory approvals throughout the world has been daunting. It helps now that we have the EU [European Union] countries. Gradually they will coalesce to have a single regulatory system.

Hughes: Is there a move in that direction?

Rutter: Yes, there is. And then a worldwide strategy for approvals. I'll give you an example of what I consider just over-the-top regulatory control. When meningococcus C vaccine was developed, Chiron carried out a trial in Britain and also in Canada. The vaccine was given to five or ten million people, and the consequences of the vaccine were known. That is, it was highly efficacious, and there were very few side effects. Still, the FDA required another trial for safety.

Hughes: At Chiron expense.

Rutter: Of course, at Chiron's expense.

Hughes: And what was their argument?

Rutter: We hadn't tried it on a U.S. population. The approval in England had gone rapidly, and we had all that data, but it wasn't done according to a regular regulatory strategy. So it's this mixed, bureaucratic application of regulatory principles. The cost of human lives and loss of productivity is staggering compared to risks.

Without a given target of protection and a way to measure effectiveness and therefore project approvals, companies are going to have a hard time investing because they don't know the barrier over which they must jump. In drugs, you just have to surpass by a statistical margin over the last best treatment. In vaccines, some people, including outstanding scientists, believe you have to get close to 100 percent protection in order to have a product, and that's

particularly the case with HIV. The two concepts don't make too much sense, not only from the standpoint of the regulatory process and development process, but from the standpoint of the people suffering from disease. Regulatory agencies demand a high level of protection, but at the same time, many people are dying. Nowadays, it's frequently impossible to test in the United States because in an area where the population has received another vaccine you have to go to some other population.

Hughes: Does government regulation threaten to dampen one advantage of the biotech industry, namely, its innovative power?

Rutter: Well, for sure, the regulatory risks are there, but there are still small companies devoted to vaccines now, and the large companies who are in the business don't necessarily have to be slow-moving and uncreative. Merck has formed a partnership with a small company, CSL, who developed the papilloma vaccine. The same thing is happening with SmithKline for another papilloma vaccine. I would say there's no good reason why Merck or Sanofi-Aventis or SmithKline aren't inventive in this field. In fact, they have sought frequently, through in-licensing and so on, to develop their vaccine program. Arguably, the hepatitis B program at SmithKline saved the company. So I don't necessarily see biotech and pharmaceutical companies as being naturally segmented into creative and noncreative. Biotech companies, by their very nature, have to have something special or they don't get any funding and will fail.

[interruption]

Hughes: You said that hepatitis B was a major basis of Chiron's IPO [initial public offering] in 1983. It was a short time from initial company formation to an IPO, was it not?

Rutter: It was a very short time, for sure. This was due to the fact that the market became strong and opened up dramatically, making it possible for young companies to enter the market. Besides the possible early development of the vaccine for hepatitis B with Merck, we had a number of other programs—the diagnostic programs and other programs associated with things like cytokines and growth factors that were innovative and generated revenue.

Hughes: And interferon, which was so hot at that time?

Rutter: No, we were not involved in working on it at the discovery level. We only got involved after we acquired Cetus in 1989. Interferon was for a time thought to be the ultimate solution, a flash of insight and a silver bullet, so to speak. Unfortunately, it didn't turn out to be so.

Hughes: Maybe it never came to be, but an annual report said Chiron had a contract on the interferons. I was interested because the interferons were so hyped as cancer cures for a period in the late 1970s-early ‘80s.

Rutter: We didn’t have a specific discovery program on interferon. On growth factors and on insulin, yes. We had a program with [Novo] Nordisk. So we had a number of projects, and that was related to the portfolio we presented for the IPO. But with the development of the hepatitis vaccine and a straightforward strategy for the production of particles in yeast, we saw the opportunity to move to other vaccines and of course hepatitis C. There was a discovery program where we saw invention as being a strong component of our repertoire.

When we formed a true joint venture with Ciba, then the core issue for the joint venture was how to develop a business and what vaccines to focus on. Ciba-Geigy had made the decision earlier not to get into classical vaccines, which were, as they saw it, low profitability, standard, generic vaccines. But they took another position, as I mentioned, with respect to these new vaccines. At that time, we called them biocines and formed the Biocine Company, under the impetus, as I said, of Jack Nüesch. The choice of what vaccines to develop, how to develop the business, was an area of common interest, and there was a lot of interaction, in fact quite wonderful interaction, between the companies.

Due to the insight and recognition of an opportunity by a key business development person named Richard Williams within Ciba-Geigy, it was gradually accepted that regardless of our focus on new high-technology vaccines, the vaccine business itself had its own business case. So while we were waiting for the new vaccines to develop, we ought to get into the business, and there was no time like the present. At that time, as well, the classical vaccine businesses were languishing, businesses which had followed from the work at the beginning of the twentieth century by [Emil von] Behring, by [Achilles] Sclavo, by [Shibasaburo] Kitasato.

Hughes: And Louis Pasteur.

Rutter: Well, these were protégé’s of Pasteur, except that Pasteur didn’t really lead the early work of protection, which was done by those three folks. The development of the diphtheria vaccine was the vaccine which got the Nobel Prize for Emil von Behring. The work a hundred years ago of Behring and Kitasato, and also Sclavo, on the development of antibodies in horses, and then the development of external strategies for vaccines had, as I mentioned, the net consequence that most countries of any size, in fact virtually any country of size, had developed their own little vaccine business as a strategic defense against weapons, but also in the context of a world that could be fragmented at any one moment. Then the absence of a vaccine supply would put the whole population at risk.

Richard Williams recognized this fact and, in discussions with me, began to consider various alternative approaches to building a business. Among them was Sclavo, which had been a family business and then acquired by the [Italian] government, made part of a big conglomerate called ENI, then by the bank, Monte dei Paschi in Siena, and finally was owned by an Italian entrepreneur named Marcucci, who owned a number of properties including a television channel. That was one potential business. The other potential business was a Canadian company, Connaught Laboratories, owned by the Canadian government, that had been formed initially at the time of the discovery of insulin. It was a conglomerate like many of these other companies that did vaccines. It also produced biologicals like insulin and also diagnostics, separate from the chemical business. Connaught had those two businesses. After discussion and after we formed the joint venture, Ciba agreed to support the acquisition of one of these companies. Our first target was Connaught, which was up for sale. It turned out to be a very competitive situation. We worked on the acquisition for the best part of a year. A few times a month, over the weekends, I would go to Toronto. Richard Williams would also come from Basel. We would be talking with the people at Connaught and discussing with the Canadian government about our role and what we would do with the business. As it turned out, there were several bidders, but the key bidders were Merieux and Ciba and ourselves. There was an intense bidding process that resulted, and the control of the bidding for our side was the head of the pharmaceutical division. However, it was mostly delegated to Richard Williams and me. The financial deal we had was that Ciba would put up most of the money, in fact, ninety-five percent of it, and we would put up five percent of the money. We would end up fifty-fifty by a complex process which would involve paying back over time to finally achieve fifty-fifty. So it was a great deal for us, and there was an incentive to get the deal done.

As I said, the bidding was intense and involved dealing with the complexity of Canadian government, especially the French side. I spent many days in Ottawa and also in French Canada, particularly with one of the major funds in French Canada, the Caisse de depot, that had a significant bloc of shares. In the end, the bidding proceeded. When the value reached something like 700 million Canadian dollars, then Merieux raised it a couple hundred to a billion, and we agonized over whether to increase the bid. I thought long and hard; it was enticing, but ultimately I didn't [raise the bid]. Too many suppositions and assumptions. I finally was against it, and we dropped the bid.

Hughes: You thought it was overvalued?

Rutter: We thought it was overvalued.

Hughes: You, William Rutter.

Rutter: Yes.

Hughes: That was the basis of your opposition.

Rutter: That's right. I think because it was a "strategic bid"—in quotes. Richard Williams, in particular, would have bid further.

Hughes: For control of the market, you mean?

Rutter: Yes, because of the advantage of getting to the market.

Hughes: Why wouldn't that have been as important to you, too?

Rutter: Well, because there was no advanced technology. They didn't have a unique position in the market, although it turned out to be quite a good position. But John Orsinger, the head of pharma, got into the bidding in the last stages. He was a key player, and he rightfully was conservative and a tremendous, clear-thinking, analytical person. I got to appreciate him.

Hughes: Who ended up buying Connaught?

Rutter: Then bioMerieux bought it, but it was such a heavy financial burden and they made so many commitments that they lost control of the company. They eventually elected to sell the entire vaccine business to Rhone Poulenc, now Sanofi, to the great distress of Charles Merieux, the scion of the Merieux family, and to Alain Merieux, his son, who now heads bioMerieux.

After that failure, we were still on the hunt and continued to look at various alternatives, and one of them was Sclavo. Incidentally, Merieux was also interested in Sclavo. As we know today, Alain Merieux himself worked at Sclavo. He loved Siena. He would have immediately chosen it. But I think the head of the business, Jean François Martin, who eventually was the head of our vaccine business, was working for them at the time. Martin's decision to go ahead and make the final bid resulted, I think, [in being separated from Merieux? (garbled)]. Ultimately, we offered him a job, which he accepted.

But back to Sclavo. Then we began negotiating acquisition of Sclavo, which was one of these complex biological businesses made up of a diagnostic business, a blood-product business, and a vaccine business, all operating from the same general site in Siena—gorgeous site, a beautiful place, for sure, and a historic business. Unfortunately, however, none of the businesses were profitable. The negotiation began first with the CEO of Sclavo and getting to learn more of the business, and secondly dealing with the owner at that time. Marcucci had acquired it from Montedison. At one time, by the way, Dupont owned 50 percent of it, and Gregory Lawless, the person who eventually was the president of Chiron, ran that business for Dupont. The negotiation with Marcucci was helped greatly by Sergio, Ciba's executive head in Italy. Sergio knew the Italian way and established a good relationship with Marcucci.

Hughes: What is the Italian way?

Rutter: Well, I'll give you an example. We began to negotiate with Marcucci at one of his resorts, called Il Ciocco, which was a mountainous resort that could be reached conveniently only by helicopter. As I recall, we began negotiating at three o'clock in the morning after being liberally plied with vodka or some other loosening agent. It was a very, very complex negotiation. And here's where Ciba-Geigy was absolutely essential because they had a division in Italy. They knew how to handle Italian finances. They knew, in particular, the problem of dealing with taxes. Eventually, we bought the business for about 120 million, including those wonderful buildings, plus some new buildings in Rosea [Italy]. We were able to extricate the vaccine business from the diagnostic and the drug products businesses.

Hughes: So you bought only the vaccine business?

Rutter: Yes.

Hughes: Beautiful buildings because they were old?

Rutter: Well, centrally located, and they were old. There was one new building on campus. There was a possible new development/manufacturing plant at another location, Rosea, outside the city. But it was very close to the walled city of Siena. It's still a historical place. But like many of the other diagnostic organizations, the employees were very focused on their programs and defensive against any of the other competitors, particularly against Behringwerke, the German company with a similar business. They had a small fraction of the market, even in Italy. Later it became clear that their manufacturing didn't meet international standards, so all of the processes had to be changed, in fact, several times. But we became committed to the business and recruited a previous Ciba person, Mario Lorenzoni, as the CEO. We also involved Dino Dina, from Chiron, who eventually took over the vaccine business.

Hughes: Dino Dina was already at Chiron?

Rutter: He was at Chiron and eventually became vaccine head.

Hughes: But unconnected with Sclavo?

Rutter: Yes. He was made head after that. He didn't participate in the negotiations with Sclavo.

Later, Behringwerke, the classic German vaccine business, became available. It was a division of Hoechst and previously had been part of Krupp Industries, the enormous German enterprise that was known for its steel making and was dissembled after World War II. After the war Krupp was split and formed

Hoechst, Bayer, and BASF. Behringwerke finally ended up with Hoechst. But as a biological entity, it really was quite isolated from the key chemical strategies in the pharma business and was really an anomaly. So they were prepared to sell it, provided that the employees were treated well, provided it would be part of an ongoing concern. When it became available, it was also obviously a complement to what we had. At that time, Behringer had a larger market position compared to Sclavo in the major countries in Europe, and with rationalization of the vaccines, why, they formed a good commercial business. This happened, actually, after the Ciba deal, so Ciba was not involved directly in the acquisition of Behringwerke. We did this by ourselves. It was a very good negotiation, with Uwe Biker. Mary Tanner, an excellent investment banker of Lehmann Brothers, represented Hoechst. Mary is the wife of Fred Frank, who was responsible for putting the Chiron/Cetus deal together. Subsequently Mary, Fred, and I have become great friends and nearly formed an investment/management group together.

[Tape 11, Side B]

Rutter: We were ultimately able to obtain Behringwerke, despite the fact that we did not make the highest bid. The decision was based upon the belief that the future of the company would be better in our hands. We developed a plan for dealing with the employees collaboratively with Behringwerke. Indeed, we became quite committed to Behringwerke, and they became a key component of the vaccine business. It was a fascinating institution. It had the original offices of Emil von Behring and all the accoutrements of his Nobel Prize—a source of great pride and also a symbol of challenge.

Hughes: You mean no layoffs?

Rutter: Only moderate layoffs.

Hughes: That was the agreement?

Rutter: That was the key important part of it. We had established a strategy for dealing with layoffs, but one that would keep Behringwerke in Germany, that is, we wouldn't consolidate into the Sclavo site. And also it was because they felt that our novel vaccines could be developed over a period of time, and therefore they would be a sustainable business in Germany. That might not have happened with the other major businesses where consolidation into headquarters would have been the usual strategy.

Uwe Biker, the Hoechst representative, was a very good strategic thinker and contributed, I would say, very significantly to the concept. But that biological business in Behringwerke, which was about $2 billion at the time, needed to be fragmented into diagnostic business and, separately, the vaccine business. Eventually Dino Dina was appointed to head the vaccine business. The

remainder of the Behringwerke business was reduced to a residual business which involved biological products.

When we had the problem of integration of these ongoing businesses with the U.S. business, which had yet to produce a vaccine on its own, we put all the technology behind it. Then each of the processes, whether in Behringwerke or in Sclavo, had to be redone because they didn't meet international standards. We had a problem also in managing the German organization and the Italian organization, because each was parochial, with its own culture, and wanted to defend its territories. The two, although superficially friendly, were fundamentally competitive with each other. We chose Dino Dina to head that group. Eventually the whole business was run by Dino, with Lorenzoni being in charge of the Italian enterprise, with representatives from Behringwerke.

Hughes: How well did that work?

Rutter: Well, coordination was a problem, for sure, and trying to deal with the problems of approved vaccines. Each of the companies had competitive products—flu vaccine, for example, and different versions of the childhood vaccines. But as was the case, once one gets regulatory approval, the approval is usually grandfathered into the future and has continuing proponents. So usually one continues to maintain these different lines that deal with the same infectious agent. We had two or three different products in flu. We had two products in rabies and different childhood vaccines. So organizing the two programs and fitting them into a commercial organization was definitely a problem. However, the Behring group is one of the best-known companies in Germany, and Sclavo maybe only slightly less so in Italy.

Both of these companies then provided a very strong base in Europe and fundamentally needed advanced-technology vaccines. The research programs, of course, focused on our technology and our own programs, complemented by the research, largely in Italy, focused on pertussis, a very common pertussis vaccine that was developed by Rino Rappuoli. However, there were intellectual property problems, and pertussis really didn't see the light of day as soon as we had planned. It is quite common that a vaccine doesn't see the light of day. Over a period of time, the production problems were solved, the company became modestly profitable, and they represented a good base for selling in Europe and other parts of the world, even in two separate locations. Then, as I said, herpes, which was the first new vaccine after hepatitis B, didn't work out. A big deal, and people began to lose confidence in the vaccine business.

At a certain time, there was discord between Dino and Mario Lorenzoni, and Dino became, let's say, unhappy in his relationship with Lorenzoni.

Hughes: Was it a scientific disagreement or was it a personality problem?

Rutter: It was a personality problem and a business problem, an organizational problem. It was, in part, based on the great distance between the two. The Sclavo organization was larger and was much further developed operationally than Chiron itself. For example, it manufactured several vaccines. So a fractious relationship resulted, and it was a significant management issue. Eventually the two became incompatible. In a confrontation, Dino tendered his resignation in protest and under unfriendly circumstances. I accepted his resignation. Subsequently, Dino formed a vaccine company called Dynavax that has developed a more potent hepatitis B vaccine.

Hughes: What impact did that change at the top have on Chiron's vaccine business?

Rutter: Well, then Mario Lorenzoni took over in the business, and subsequently, after Mario, after the Ciba deal, Martin from bioMerieux was appointed after Dino. He was an acknowledged leader in vaccines. Martin lived in France, and we had a business in Italy and Germany, so that partially worked. Our programs grew, but did not transform the industry, as we had hoped. I think I've told you the rest, the story of the failure of the herpes and the long struggle to develop HIV and hepatitis C vaccines. Although the vaccine business achieved significant magnitude, the strength of the programs was always in high technology approaches, especially the development of good adjuvants. The first adjuvants that were used, advanced adjuvants, came through our programs.

Hughes: Are the adjuvants different in the case of AIDS and hepatitis C?

Rutter: Well, they're different vaccines. We had a major adjuvant program which formed the basis of a potential increased level of production of antibodies from any vaccine, including mucosal vaccines and systemic vaccines. That program, especially in the last ten years, has been a difficult one for Chiron vaccines because we had to consolidate everything to meet international standards. This required extensive reformulation and regulatory approvals. We finally did it, but it is not a profitable business. They are still waiting on the development of the HIV vaccine and hepatitis C vaccine.

Under Rino Rappuoli's leadership, there has been a major development of a vaccine to cover all types of meningococcus, which has just been recently been approved. Indeed, the whole meningococcus vaccine program was developed by Rino Rappuoli and his group in Siena. Rino eventually became head of the vaccine program and was elected as a foreign member of the U.S. National Academy of Sciences. The program was attenuated by Sean Lance after we left and only partially recovered in the Novartis organization.

Hughes: Have the recent problems with the flu vaccine leaked over into the business as a whole, so that Chiron's reputation as a vaccine business is tarnished in all areas?

Rutter: I can't answer that because I've not been there, and I haven't seen the reaction of the market. But certainly from a distance, it's clear that Chiron's reputation for vaccine manufacturing, and especially for flu, has fallen. Now this second problem in Germany just exacerbates that problem.

Hughes: Is that just coincidence that there were two separate contamination problems?

Rutter: The contamination problem is in flu, in general.

Hughes: Why particularly flu?

Rutter: That's because the current flu vaccines are made with eggs, and one has the problem of millions of eggs coming in to be incubated. This requires fastidious quality control since the incubation of the virus is in the eggs. It's an open environment so you're going to get some contamination. It's always been known as a problem, especially when you do large numbers of eggs. Chiron obviously strained the process.

Hughes: By trying to make so many doses?

Rutter: By increasing production and speed of the production of the components of the vaccine. But the issue, of course, is whether Chiron is going to focus on vaccines or not. I think that is a central strategic matter, which is related to the focus on biopharmaceuticals, which was a result of the acquisition of Ciba. But that's another story. Okay. I've got to go.

Hughes: Thank you.

[End of interview]

Interview 6: July 30, 2005

[Tape 12, Side A]

Hughes: I'd like to hear today about the division of labor between you and Ed Penhoet, in terms of who did what on a daily basis at Chiron.

Rutter: Well, generally, Ed and I and Pablo Valenzuela discussed all significant issues, and we ran the organization as much as possible by consensus. But I was the ultimate decision maker if there was a real difference of opinion. Ed and I focused more on management of the company and business and strategic matters, and Pablo and I focused on research, which was, of course, a major activity of the company. But really there was a great deal of operational and strategic discussion between us as well as multiple two-way discussions. I was more science-oriented at this time than Ed, so Pablo and I worked closely together on strategy and execution of R&D. I was interested in the details of the science, and Pablo and I talked frequently, several times a week. At least once a week we had a scheduled R&D meeting in which each of the projects was discussed in detail, that is, what happened during the week at the experimental level. Most of the time it was an all-hands meeting. Ed also participated actively. It was important that he integrate the strategy and research progress of the various projects in the context of providing a coherent picture to outside investors and other interested parties.

Now, with respect to Ed and I and managing the overall enterprise, we worked together as a team. But there was really a practical segregation of responsibilities. Ed, as the CEO, faced the outside community and dealt with overall communication with investors. Since we had become a public organization so soon after we had started operations as a company—I think in less than two years—this became a predominant activity, and it also reflected his unusual talents. Ed is a superb communicator and enjoys that aspect of the job. I think he is the most talented individual in the industry in explaining both the state of the science, the biotechnology industry, and Chiron. His presentations reflected well on Chiron. He maintained an excellent relationship with analysts. He always had a good sensibility in presenting the company and articulating the key issues. He provided a balanced view, not overselling and certainly not underselling our strategy and performance. Ed has excellent taste and is a wise person. He is never arrogant and never seems to "lecture." He always shines the light on someone else, emphasizing their contributions and in this way always had a very positive effect on morale and overall company spirit.

Internally, Ed was genuinely interested in the social organization of the company, and with individual attitudes and behavior, and building consensus in the various teams and in the company overall. For example, early on, he led an internal group which focused on elaborating the mission of the company, and out of that dialogue came a statement of ethics. He brought in one of the

previous vice-presidents of Levi Strauss and also Jim Wilson, the previous president of Syntex, to advise, and lead internal discussions about building a unique culture. His activities in this area were exemplary, and he had a great positive effect on building the Chiron culture.

Hughes: Mission in a broader sense than what one would see in a prospectus?

Rutter: Well, developing a bottoms-up mission statement, not top-down. I was more a top-down guy, and I would try to sort out the overall issues, matters of principle, and lay out an overall set of strategic goals, and present the philosophy behind the goals in terms of science/business goals, and our unique opportunity to influence human health on a worldwide basis. Ed had both the patience and the wisdom to understand, it's really important to develop a participatory perspective as well and get buy-in to corporate goals. This results in an open dialogue on the programs of the company and an increased commitment to them.

Every company has some kind of culture. I think ours was particularly vibrant. We had an unusually competent and committed group of colleagues. When I meet former employees today, almost to a person, they mention that Chiron was the best job they ever had and the best group of colleagues. Ed certainly played an important role in establishing that culture. So did Pablo, and I also was enthusiastically committed to establish good human relations at all levels. Chiron was certainly an open place. We had company-wide meetings and groups meetings on special projects, and a range of activities that engendered interest and support. On the other hand, we were dead serious about doing important and unusual things. We had a fabulous work ethic and an exceptional group of committed individuals at all levels, even down to the janitorial staff.

Hughes: Why wouldn't you have known that developing a participatory culture was key, having been chairman of a department for all those years?

Rutter: I was sensitive to it. We also had excellent relations and a wonderful sense of community at UCSF, but it came naturally by having a common set of objectives with many collaborations. As a result of that experience, I felt this came naturally in a company as well in the course of setting up great projects and working with the people who executed them. But it was not a priority for me to work deliberately on a program to develop corporate culture and to approach the problem in such a disciplined way, that is, to engage others with experience and learn from them. Nevertheless, it was an important issue, a necessity really, in an organization in which there are segregated and diverse roles and disciplines, and information flow is necessarily managed. Further, the size of the organization and geographical locations rapidly made corporate culture an aspect of productivity and personal commitment and fealty. A company has to have a coherent set of goals and diverse functions supporting those goals. Ed took on this role naturally and with great enthusiasm and

seriousness. This is one of his great strengths. He is naturally inclined to be inclusionary, thoughtfully articulate, and always extols the virtues of others while deflecting credit from himself. These qualities made him a fabulous CEO.

Hughes: Were you surprised to find this in Ed?

Rutter: No, not at all. I had known him since he was a graduate student. He was a social integrator from the beginning. It is one of his major talents, and it is evident today. It was also true at Berkeley. He was widely acclaimed as the best teacher and the one who brought the disparate elements in that [biochemistry] department together. This was a significant factor in choosing Ed, both as a business partner and as a CEO. He in general has a great tolerance for different points of view. He has an outstanding talent for solving problems of discordancy. He is certainly very sensitive to their existence and persistent in solving them, if he can. He's more effective in dealing with such matters than anyone I know. So naturally, he led in building a corporate culture and human resources. He also was responsible for accounting, finance, building infrastructure and external relationships, and he handled them superbly.

Hughes: As CEO, it would be expected that the Chief Financial Officer would report to him, right? He wouldn't report to the chairman.

Rutter: Yes, of course, the CFO did report to Ed from the beginning. However, there are traditional structures and there are unique situations in every organization. There's no absolute rule about who does what or how tightly the organizational operations are tied to the typical structural archetype. Certainly, we did not have a textbook organization. For example, I would take the lead in strategic negotiations, many partnerships, etc. Of course, in all of those I worked closely with Ed and Bill Green, who became an outstanding corporate attorney. I realize that many chairmen only deal with strategic matters and not with operations. That is, there is a distinct separation between overall strategy and operations. Some chairmen (and boards) act only to monitor the performance of the CEO. Others are deeply associated with the operations and day-to day-operations. Our organization was more interactive. I dealt with strategic matters and the operational details at two different levels. I usually led overall strategy and negotiating deals, and as a team, Ed, Bill Green, and myself were pretty good.

Hughes: This arrangement was true even before you were spending more time at Chiron? In Chiron's early years, you were chairman and also director of the Hormone Research Institute at UCSF.

Rutter: Even during the early days, for sure. I came over to Chiron every weekend and many evenings during the week. I knew what was going on in research. There was never a period in which I was distant from the strategy and

operations of the company. I knew in detail what was going on, especially in research and development, but also at the business level. Many of our best and enduring agreements occurred during that time

Hughes: Can I ask you to compare yourself to Genentech's Herb Boyer in the early days? Both of you had demanding academic positions. Do you think you were relatively more engaged in Chiron than Herb was in Genentech?

Rutter: You know, I really can't say because much of what went on at Genentech, and particularly the division of labor between Herb and Bob [Swanson] was obscure to me. But knowing Herb and Bob and by reputation, my guess is I was much more involved in all aspects of the business. In the beginning, Herb must have been active like I was, or even like Pablo, in the day-to-day management of research. But I think Genentech rapidly recruited good independent scientists. I think they recruited David Goedell as director of research early on. David Goedell is an excellent scientist and leader and might have had a role like Pablo's. All of the top three at Chiron, Ed, Pablo, and I, were scientists, while Bob Swanson at Genentech was trained in business, and I think that Genentech's board played an important role in strategy as well. Our board was small and supportive. Jean Deleage, as an investor, was the only key financial advisor, and he was supportive and helpful but never got involved in science or business strategy at an operational level.

I was directly involved in the development of the strategy of the company from the beginning. Although both Ed and I wrote the initial tripartite strategy, it was largely my view that drove that initial focus and the programs emanating from the central ideas. For example, I wrote the initial business plan by hand. In those early days, I played a strong role in business strategy. I would participate directly in the major negotiations and in the internal organization, establishing divisions oriented to one function or another.

Hughes: What expertise were you relying on? I'm thinking particularly of your consultant roles with Merck and other companies earlier on.

Rutter: I think I did gain a lot from the years I consulted with Abbott. In the final several years, the '60's and early '70's, I had direct interactions with the top-level executives at Abbott on each visit, and that broadened my perspective substantially. I also gained some experience and perspective on strategic thinking. After several years, I developed my own ideas about the strengths of science in relation to the Abbott business, and I had quite extensive discussions with top Abbott executives, especially with the CEO, Ted Ledder, who was a change agent at Abbott. I was one of those who strongly supported setting up the diagnostic division at Abbott and spent considerable time in elaborating the reasons for this commercial division. Abbott scientists at the time were good at measuring and analysis. They considered themselves fast followers, not innovators. In fact, they did not have a good record at developing new drugs. Hence I believed they would be very good at

diagnostics. Eventually, Abbott set up the division, which developed into one of Abbott's strongest divisions. However, all that experience as a consultant didn't really prepare me for the responsibilities and duties associated with a company or with negotiations per se. The consultations were largely focused on specific scientific programs and science strategy—building value through science programs.

Hughes: But you had a quasi-insider's look at how these companies were run that must have given you some experience that was helpful for Chiron.

Rutter: Yes, for sure, because I saw firsthand the limitations as well as the strengths and also the struggles of the research organization within the corporate structure. I think I gained some insight into what not to do. Especially at Abbott, I had a pretty open relationship with the management of the company, especially regarding the issues that were involved in managing specific programs, both individually and collectively.

I knew something about the complexity. In my role as chairman of the UCSF Department of Biochemistry and Biophysics, and representing that department's interests in the context of all the competing needs of the other basic science and clinical departments, there was perpetually a need for give and take. It was necessary to pay attention to the development of the entire organization and yet pay particular attention to the success of Biochemistry/Biophysics—basically to develop the science to the highest level and make it recognized as one of the great departments, at the national and international level, but also foster collaboration and collective success of the medical school. I think we had some success at doing that at UCSF.

Ed always sought to achieve a balanced accommodation of all interests in our collaborations. I might have been more inclined to have the balance a little more shifted in our favor.

Hughes: [laughs] It is not difficult for me to believe.

Rutter: I like negotiation, the strategy and the tactics associated with the negotiation process. I learned very quickly that we had to think in those terms if we were to be successful in a business based on collaborations and licensing. I think I already have mentioned the negotiation with Merck on hepatitis B. It was a tremendous lesson, but we also paid a high tuition for the schooling. So both strength of will and a sense of strategy and analytical aptitude and a quite specific understanding of the science and its competitive position, I would say, were what I tried to bring to the negotiation. On the other hand, let me say immediately that during all the negotiations, Ed and I worked as a team. He was very sensitive to the attitude of other folks. He always established a friendly relationship, which is crucial in contemplating any working relationship. So in gauging where they were and where we were, we were better as a team than acting alone. Nevertheless, I more or less led most of the

negotiations. I was pretty aggressive in supporting/defending our case. I think partnerships and corporate relations were one of our strong suits

Hughes: So, simplistically, were you the tough guy and Ed was the conciliator?

Rutter: Well, maybe there was a little tendency in that direction. But negotiation with us was never a situation involving the bad guy and the good guy. We always kept the discussions respectful, friendly, and with good humor. We never developed a we-vs.-they style. In fact, quite the opposite. Certainly my style was never to be tough in the sense of being obstinate, but rather to develop a rational basis for our position. I didn't want to foster a covert we-vs.-they attitude. I also wanted visibility in the development and recognition in the product itself. So both of us tried to establish very good relations with others, and I think we were quite successful in doing so. At the level of relationships, we were a good team. I came across as a scientist, having been involved in the science of many of our initial projects, and I could communicate the scientific issues and strategies for business development well in relationship to prospective business terms. So could Ed. But he had less of a scientific bibliography, and he came across as a more science-oriented business person and would deal with implementation of the projects.

To be quite specific, I conceived of the fifty-fifty deal in which we produced the product concept, and our partner supported the project monetarily, and then we split the value fifty-fifty. We both espoused it and built the philosophy behind it at all levels. Clearly it was something that we wanted to espouse as a principle because if we started to break the rule for one, the concept would deteriorate. All the major companies preferred equity control over the joint venture or business. The initial response from other companies always was, "If it is a partnership, why are you worried about one percentage point or two in equity? It's only rational that the big company providing the money would take 51 percent, and the smaller company, like Chiron, take 49." Well, yes, but the difference between 51 percent and 49 is the basis of legal and practical control of the program. It is a way down the slippery slope when it comes to determination of the principles of operations and the final goal for the business. By maintaining categorically that we wanted fifty-fifty deals, we eventually got them. And it worked to our advantage dramatically, both in the sense of developing our organization and competence that is required to play that role, and the commercial position that we had as a small company. Of course, it also brought with it the challenge of execution—we needed to pull our own weight. We needed to be successful at the science/medical level. We wanted that challenge.

Now, having said that, fifty-fifty was interpreted differently in different circumstances. I mentioned before that the Ciba relationship was a fifty-fifty deal. It was a fifty-fifty business. We operated it. They understood the principle, and we understood the principle. And we negotiated a deal that really was good for both parties. By that I mean, the original fifty-fifty deal

with Ciba on vaccines (Biocines) was much more like a true fifty-fifty deal. We shared strategy and execution at every stage. But in J&J, fifty-fifty was defined differently: we were responsible for all the technology, and they were responsible and controlled the marketing and selling. Then we shared in the profits fifty-fifty. That was a fifty-fifty business; it wasn't a fifty-fifty deal at all levels of execution. So we tried to be pragmatic, but it was in the end not the best for either company, and we should have held to our guns.

Hughes: Why bad for J&J?

Rutter: Bad for J&J because in the end J&J never was viewed as a real partner. Our interests were not totally aligned, and we had serious issues between us. We even went to legal arbitration at one point—a bad sign. So in the end, the top-level executives were interested in acquiring Chiron, and we were quite attracted to the corporate philosophy and culture of J&J. In addition, we had excellent relationships with the top executives of J&J, Burke, Clair, and Wilson. We thought that if we were to accept a bid from J&J, it would be in the context of forming a separate operating company within the framework of their multiple-business conglomerate, that is, a separate business within J&J. This would allow us more intrinsic freedom within the larger enterprise, as opposed to Ciba-Geigy where everything is consolidated into a single pharmaceutical enterprise which is managed at the board level. At the time, Ciba was quite a broad company. It dealt with everything from paint, carbon fiber, photographic films, as well as pharmaceuticals. We realized that on the operational level, integration into the two companies would be quite different.

Hughes: Did the possibility of acquisition even get to a discussion point?

Rutter: Yes, indeed. Right at the end, Jim Burke, David Clare, the chairman and CEO of J&J, and Bob Wilson, the vice chairman of J&J, moved aggressively to acquire all or part of Chiron.

Hughes: What happened?

Rutter: Well, it was too late and too little. I think that by that time, we had a very good understanding with Ciba-Geigy, and the combination of their putting some of their assets into our business, and the overall terms, including quasi-independence, were unbeatable. We also had developed an extraordinary relationship with the Ciba-Geigy executives, particularly with the chairman, Alex Krauer, the head of the pharma business, Jean Orsinger, and the director of biological science, Jakob (Jack) Nüesch. This understanding would have led to a wonderful business had Ciba-Geigy remained independent. We simply didn't conceive of the possibility that Ciba would not remain independent. Had the merger not happened, we would be a different company today, and so would they. So those are two examples.

Within the company itself, I explained a little bit about what Ed's role was. But then we had three divisions. I paid a lot of attention to research, and Pablo and I discussed research strategy and the particular approaches. Pablo in turn was in full control of the planning and execution of the experiments. All three sat together. We knew the key people personally, their talents and idiosyncrasies, and how the programs were going. In the eighties, we had detailed research discussions on Saturday mornings. Later, the research organization increased to a size that required more divisionalization. Besides research, I also took a lead role in diagnostics and vaccines. After the J&J deal on diagnostics though, Ed took the lead in managing the relationship with Ron Gelbman and the J&J the joint business, while I was the key person with Ciga-Geigy and vaccines. After the Ciba-Geigy deal, however, I paid specific attention to the diagnostic division.

Hughes: Lacey Overby headed diagnostics in the beginning, is that right?

Rutter: Diagnostics, yes, especially in research and development. But then it became a pretty big division. After we acquired Ciba Corning Diagnostics, Greg Lawless became head of the division.

Hughes: Was ever yours and Ed's lack of hard-core business experience a detriment? Neither of you had been to business school. You hadn't had any formal training in business matters.

Rutter: Before I answer that question, I want to continue. For a while, we had an ophthalmic division, and Ed took over the leadership of the ophthalmic division.

Hughes: That was early on. Because of the growth factors?

Rutter: Yes, the ophthalmic business was based on the putative role of growth factors in healing defects of the eyes. When these did not provide a strong therapeutic signal, the business shifted focus to refractive errors of the eye.

In the biopharm area, as we began to integrate Cetus into the organization, Ed took on the substantial role of integrating what was a very complicated and heterogeneous organization into Chiron. He tried to establish a balanced integration of the companies, calling it a merger rather than an acquisition. Hollings Renton became the president and headed the therapeutic division, such as it was. I led the negotiations with respect to Betaseron. At first, we only had a manufacturing arrangement, and so we negotiated a business relationship with Berlex, eventually Schering Corporation. We had a long continuing negotiation with Lutz Lingnau, the head of the American business for Schering. It never developed into a completely successful relationship

Hughes: Because of personalities?

Rutter: Not really; the relationship was not prickly. I think I had good personal relationship with Lutz Lingnau, and so did Ed, for that matter. But it was the disparate interests and objectives of the parties. Again, this was no fifty-fifty deal. It was a situation where they had marketing rights, and we got a percentage of the revenues from the sales which decreased over time. We added a lot of value to the program, as was our general approach to things. Whether we were fifty-fifty or not, we always acted as though we were fully committed to the program. We tried to develop the best research and commercial program as a result of that.

Hollings Renton assumed leadership of the biotherapeutics program and reported to Ed. But when it came to the scientific details of the program, I became involved as well. We tried to be efficient, and I think we were, while still getting as much oversight as practical on the programs themselves. On the commercial side, as we began to extend from the U.S. to Europe, Ed became involved in the management of the group, and I participated in the analysis of the scientific and technical details of the programs themselves.

Now you asked a question: Was our lack of business experience ever a detriment? Well, yes and no. I believe that early on when it came to the negotiations I've already told you about our naivete and lack of experience in the Merck negotiations where we were at a distinct disadvantage. So in those early days, there's no question we were to some extent naïve and were at a distinct disadvantage. I believe that Chiron put more emphasis on ophthalmics than it otherwise might have done if we had had a more disciplined business orientation. Once the epidermal growth factor therapeutic in the eye failed, then we might have withdrawn from the business because it was not our core competence. Further, the market didn't understand the ophthalmics part of our business. However, Chiron Ophthalmics had an outstanding CEO in Bill Link, and he had an excellent group of colleagues who have since collectively helped to change the world of ophthalmics. So we supported the business, believing there were some outstanding technological approaches coming that would change ophthalmology. And there were. Chiron Ophthalmics pioneered some of them, much to the credit of Bill Link and his colleagues.

We were about to realize the value of them, but in the business transition with Sean Lance as CEO and a change at the board level, Chiron sold the ophthalmics business—perhaps too soon. We were just beginning to bear the fruits of being one of the pioneering developers of Lasik, today the standard way of treating refractive errors of the eye. However, in the intervening several years we were supplying contact lenses, etcetera, clearly a volume manufacturing business which was not our core competence. We needed to be in areas where our research knowledge provided an advantage. At the time we felt, if there was a science-driven way to change an industry, that was potentially a target for us to consider, provided we had some unique approach or perspective. There was this tantalizing approach to ophthalmics with new

technologies to correct refractive errors. But also we wanted it to be a self-sustaining business.

Hughes: My impression of you and other academics is that you're looking for promising directions to push the science, and presuming the resources are there, you're going to go after them. Whereas in a business, even though the opportunities are there, it might not be the best business strategy. Chiron, as you know, has been accused of being unfocused.

Rutter: Yes, that's right, and to some extent it is a valid critique. We were opportunistic and went in directions where we thought our technological approach could make a difference. It is true that focus has become a mantra and a useful one. However, it applies to success and also to failure. As you know, many companies which have sharply focused on a single product have failed. In fact, depending on the statistics, it might be eighty to ninety percent failure! It is a question whether a company with technical advantages can operate effectively in more than one area by selectively concentrating talent in each of those areas, with the combination being stronger than a more narrowly focused organization. For better or worse, I believe the latter, provided that the organization has the management and scope of talent and can manage the resources. In principle I believe the company can be more successful because of multiple ways to win, (multiple shots on goal), and the discipline imposed by the requirement to manage the resources carefully. When the organization ceases to gain by synergy, or there is need for sharply focusing on a market/technological segment, the company can be spun off.

In ophthalmics, the initial aim of using growth factors to control healing defects of the eye was supported by strong preclinical evidence and by the importance of the problem. Having committed to that scientific program and the business concept associated with it, we kept on developing the business due to the overall competence and entrepreneurialism of Bill Link and the group at Chiron Ophthalmics and the opportunities in the area. The question was how/when to exit. We had competence and an unusual position in that industry through Link and colleagues. I think we assessed the assets carefully. But we were not experienced in ophthalmic pathology nor in the broader part of the business. There was a lot of interest in ophthalmology in those days. We became operationally and structurally committed to the business before we were certain there was a unique product entry. In the end, however, Chiron was in the forefront of technological approaches to surgical intervention in vision correction, which is a major area in ophthalmics today.

Chiron Ophthalmics could/should have become an independent company, but the market timing was not good for that at the time. The major issue was when and how to exit. In the Ciba deal, optimally, Chiron Ophthalmics should have been integrated within Ciba Vision to form a stronger ophthalmic company. We tried to execute this transaction at the end as an alternative to selling it to Bausch and Lomb. At that time, though, the decision was to exit asap for

"strategic reasons", hence its real value was not achieved. We should have insisted it be a specific part of the Ciba deal itself.

[Tape 12, Side B]

Rutter: With respect to the remuneration for our broad science program, I think we were adequately compensated. About $200 million in royalties per year comes to Chiron. It's difficult for me to say that that was an error. I think that our patent position is particularly strong.

Hughes: Even with Genentech being the first off the block?

Rutter: With the exception of those initial core patents and looking at the IP estate overall, yes.

Hughes: The Riggs-Itakura patents?

Rutter: That's right, with the exception of those patents. Our position was quite strong. Now, I wouldn't say that we used that strength as effectively as we might have. That's another matter. For example, we had the early and fundamental insight into TNF [Tumor Necrosis Factor]—the drug being anti-TNF. But we didn't succeed in developing the neutralizing antibody. That would have been a major drug. That was in part due to the very early stage in the observations and a very difficult relationship with the inventor, Anthony Cerami. So the richness of the palette created, I would say, a strategic urgency which was diluted by the several activities of the company, one of them being Ophthalmics.

Hughes: Yes, right, and the initiation of the ophthalmics program was based on another growth hormone.

Rutter: It started with a hormone, EGF, epidermal growth factor, which was shown by Rita Levi-Montalcini and Stanley Cohen (who won the Nobel Prize for this work) to be effective in growing epithelial cells, ostensibly the cells that would rejuvenate the epithelium of the eye after it had been disrupted by injury. This project turned out to be unsuccessful in part because of the extreme variability in the patient populations and perhaps in the mechanism of delivery. Both EGF and Insulin Growth Factor 1 turned out to have little value as therapeutics, at least for the indications we had targeted at the time. The EGF receptor, however, now turns out to be an important cancer target. So as I reflect on your question: yes, a more experienced businessperson might have been more disciplined about focus.

But at the same time, we and the industry were growing explosively in areas which were totally open to development. We focused on innovative programs and innovative targets based largely, but not solely, on recombinant DNA

technology. Because of the general status of the technology and the opening of therapeutic potential of a new set of targets, we tried to have multiple shots on goal, to use a common term. However, we tried to develop multiple commercial outcomes from a given target and experimental program (the tripartite strategy).

I think our programs in both vaccines and diagnostics changed the industry, both conceptually and practically. As measured both by IP position and patent revenues and businesses created, the diagnostics business was the leading program in infectious disease diagnostics and maybe diagnostics as a whole during that period. We focused on quantitative testing of HIV, HBV, and then HCV (the Hat trick), the key viruses that are typically transmitted in human blood and were the cause of enormous health burden due to the need and common practice for blood transfusion or the use of needles for self-administration of drugs.

Our strong intellectual position on HIV and especially HCV, together with HBV, and quantitative methods for detection, led to the concept of viral load, which [formerly] was an unheard of concept. Viruses were typically measured via culture, with a positive or negative result. At best, semi-quantitative results could be obtained. Quantitation led to the concept of viral load, which is really the basis not only for detecting disease but also for measuring the outcome of treatment. It is the basis for both discovery and development of new drugs, but also the basis for measuring infectivity or lack of it. It is the basis of infectious disease control. From a practical point of view, our test literally saved tens if not hundreds of millions of lives via those and ancillary tests. They essentially made the world's blood safe! Of course, I acknowledge that we did not do that alone. Other companies became involved with measurement systems different than ours, for example, PCR [Polymerase Chain Reaction]. But inevitably they licensed our technology. This was probably Chiron's greatest contribution to business and to human health.

The vaccine business I think arguably, was among the best in the industry from the standpoint of both intellectual property and the projects we were developing. SmithKline was a major competitor. Merck was a major player and was our partner in developing the HBV vaccine. We consolidated the vaccine businesses that were typically supported by the countries' own public health programs, in particular, in Germany, Behringwerke; in Italy, Sclavo. The main products were childhood vaccines and general public health vaccines. In each case, we brought recombinant methods into these programs, enhanced the quality of the vaccines, added better vaccines, such as *Haemophilus influenzae*, another vaccine produced by recombinant methods. We needed to continue to build those programs. It takes a while to build a vaccine franchise. But it continues; it has persistence.

On the other hand, we were not as strong in therapeutics as we needed to be, especially in small-molecule drugs, the area where the large pharma

companies were strong. I particularly did not feel that we, or any other biotech company for that matter, had a competitive advantage in that area. Obviously we should have been very active in developing drugs for HCV and HBV. This should have been, could have been, would have been a program that we would have developed with Ciba-Geigy. It didn't happen with Novartis.

Hughes: What about the economic basis? We've talked about the tripartite structure on several occasions. Does that apply also in terms of resources?

Rutter: Well, resources, especially for clinical development, become competitive for sure. But at the research level where we were largely operating, I think they were complementary. The Ciba deal, when we couldn't have relationships with other companies because of their unwillingness to engage in our typical fifty-fifty deal, Chiron was partly owned by Ciba, and Ciba had the option to acquire the company. Therefore, prospective partners considered a possible transference of IP and products to Ciba!

Hughes: Had you anticipated that problem when you negotiated the Ciba deal?

Rutter: Yes, we considered it. We investigated this and thought we had a satisfactory legal arrangement that would allow us to work with other companies. And so did the folks from Ciba believe this, or at least they said they did. But it didn't work out that way. The business disappeared after the Ciba deal.

Hughes: Would that have changed things, perhaps?

Rutter: If I'd have anticipated the loss of the research business and partnerships, we would have changed things. I think that because of the transforming features of the Ciba deal, it was inevitable that we make a deal with Ciba. However, we would have changed the strategy by which we went about our business in the next couple of years for sure if we'd have anticipated that. But once we had anticipated it, we really had to change our business strategy. I would have then urged us to simplify in some way, either by spinning off companies, which we ultimately did, or becoming integrated more into Ciba-Geigy, where they could have taken part of our group. The latter was part of the Ciba strategy, and we would have benefitted enormously from that. We considered having a major strategist in the Ciba organization, Richard Williams, join our group. He would have been outstanding. However, circumstances precluded that from happening. When Ciba merged with Sandoz, on the other hand, that cooperative strategy vanished.

I should have pushed more for Ciba to acquire [Chiron] Ophthalmics as an aspect of the deal. I am quite sure that that could have been achieved. In fact, I tried to do that subsequent to the deal because Ophthalmics had a logical home in Ciba Vision. But Ciba Vision's vision was focused on lenses and eye-care products. However, there was a real complementarity there, which was not appreciated by the Ciba Vision people subsequent to the deal. Merging the

divisions would have helped us significantly, and them too. Bottom line: the negotiations with Ciba were intense, complex, and urgent, and we missed a strategic opportunity to clarify some of the ensuing problems.

On the other hand, in the Diagnostic Division, the acquisition of Ciba Corning Diagnostics happened at the same time there was a change in the overall financial underpinnings of the diagnostic industry. Prior to 1995, diagnostics were sold in panels. So a doctor would give you a panel of tests that included the specific test relating to the prospective disease under investigation or treatment on the supposition that the additional tests would provide new information about the patient's health status. Under the new guidelines, a prescription was specifically restricted to the tests directly associated with the disease or condition under investigation. So the revenue from the industry then based on panels shifted to individual tests. So suddenly the volume of diagnostic tests decreased dramatically, and that changed the underlying financial basis of the industry. Firms began to collapse and consolidation began because the total volume of tests decreased significantly. Chiron Diagnostics, which included the major instrument systems being developed by Ciba Corning Diagnostics, suffered during this period, in part because their sophisticated instrument systems were in the latter stages in development and had not yet become integrated in the market. So additional time and resources needed to be employed. So Chiron had a number of developing businesses at the same time, hence the imbalance in the overall business. The consolidation of all the businesses in Chiron required a period to basically winnow and focus. When changes begin to happen, frequently there is a deluge of changes, and that happened to us—the good with the unfortunate.

When I said positive and negative, I think we did a lot of things that were positive and turned out to be pretty good for us and the industry. I think selling the diagnostic business outright was a big financial success. In some respects, brilliant. It gave us cash flow from royalties without the complexity of running the business. However, I believe it was a mistake because of even higher potential alternatives. We had an opportunity to form an alliance, a fifty-fifty partnership, with Roche. It was supported at the highest levels in Roche. However, this alternative was rejected by Novartis. A Chiron-Roche partnership would have created the most profitable and far-reaching diagnostic business in the world. Further, Chiron did not acquire the Gen-Probe business which was necessary to fully develop Chiron's DNA based diagnostics business. Thus consolidation of the business into a world leading business was not carried out. I think this also occurred during a period involving loss of confidence at several levels and, importantly, a lost opportunity for Chiron. Fifty-fifty deals in research-oriented enterprises are distinctly different than the typical business approach.

Hughes: A research-oriented approach, isn't that what all biotech companies have?

Rutter: Yes, all biotech companies focus on research. But I think our business proposition and model was quite unusual and also substantially effective. I think we formulated and executed fifty-fifty deals which propelled us into the businesses that were based on the research. We didn't start with that program; it evolved from the fusion of established research of high potential in an area, not just single products, and then resulted in acceleration of the development via an agreement with an established commercial entity. We developed that model.

Hughes: What else can a young biotech company do but research?

Rutter: Obviously, our major strength in the early days was research, but there was no business based on research that existed. So we had to establish the business base on which a research enterprise could become a business, not just be a research component of a large business. So the whole point is that in this area, given all its constraints, none of the small biotech companies at the time knew how to convert to a business. The development of the business model occurred with experience. All the companies floundered at some point, but eventually great value was created by some. Later, we had some outstanding business leaders, including Magnus Lundberg and Paul Hastings, for example.

Hughes: Are you claiming for Chiron the model for doing a research business?

Rutter: No, of course not. But we did help evolve the model for businesses based on research and new technology: the tripartite business model; the fifty-fifty-deal; the integration of novel technologies with older technologies to build a business; in vaccines and diagnostics, the imposition of intellectual property on a whole field. Whereas intellectual property was known on the pharma side, on the vaccine side and the diagnostic side it was never appreciated that you could change a whole industry by having proprietary products. So hepatitis C and HIV substantially changed the diagnostic industry. Before it was a quasi-generic industry, and it was based on central lab systems–big iron. It was based on accelerating through-put of tests and the efficiency of the overall organization—great accomplishments of themselves. However, the value in the diagnostic industry is determined by the ingredients of the specialty items which have high value and are required to be in the roster of tests if they are to be purchased by the hospitals. That's how the industry runs today and probably will run [in future]: a combination of specific high-valued proprietary tests, as well as the instruments to run them.

In the diagnostic arena, perhaps the most valuable contribution was the viral-load concept, which we developed. It is at the core of developing and measuring the severity and the progress to control infectious disease. It took almost a decade to get universal acceptance of this concept, but it is at the heart of protection of the world's blood supply, for transfusion and other purposes and for the production and clinical use of blood products. Same thing with vaccines. The hepatitis B vaccine changed the industry, for sure—

the first billion-dollar product. From it SmithKline, now GSK, took over from a strong position in hepatitis B and then worked on their own proprietary vaccine products. Same thing was true with Merck. Merck did have some vaccines that were unique, a proprietary attenuated strain of measles, for example. It still exists as a proprietary product. So there were a few cases like this. But I think we led the overall approach in utilizing new technology to change products and concepts.

Hughes: Did Chiron have any therapeutic strength before the acquisition of Cetus?

Rutter: We had projects. We didn't have products. We certainly developed factor VIII. We developed the process for making insulin for Nordisk, a process which is now at the heart of the process for Novo Nordisk, the world's largest supplier of insulin. We had IGF-1 [insulin-like growth factor 1]. All represented important new advances. We out-licensed most of them. A key aspect of our program was to out-license. We had internal development programs as well. In fact, we had outstanding preclinical and clinical development teams in the company. But some of these earlier programs based on biological products were not fully developed because of a sharp focus on hepatitis C and other urgent problems.

The factor VIII product, the mini-gene, was one of the better means to produce factor VIII activity. We obtained a patent on the technology, and it's still a very good approach to factor VIII. We had a joint venture with the Ethicon Company of J&J to develop those growth factors, especially IGF and potentially others. It turned out that the initial indications didn't succeed in the clinic. And after the Ciba deal, this agreement was terminated. Most of the early products failed or had modest success, except for insulin. But even in that case the methods employed were not the initial Genentech method. Eventually several of the products found indications, among them interferon, and that compound came via a collaboration with Cetus. That interferon project had already been out-licensed by Cetus to Schering.]

Hughes: There was a drug candidate earlier than interferon that I read about in an annual report.

Rutter: We had a program on superoxide dismutase. It originated entirely within our research organization, independent of Pablo or me or Ed.

Hughes: But you must have been supportive or it wouldn't have gone on.

Rutter: I was supportive of it, for sure. The concept was good and in the end was valid. However, the research behind it led to a simplified hypothesis.

Hughes: Could you have known that at the time?

Rutter: No, but this is an example of having the hubris to embrace ideas without sufficient preliminary study in good biological models. It was a major problem in the industry in the early days. At that time, there was a surge in confidence regarding mechanisms of pathogenesis and the feeling that recombinant methods would quickly resolve many of these previously intractable problems—the low-hanging fruit phenomenon.

The target indication [of superoxide dismutase] was re-perfusion injury which is the major underlying pathology in strokes and heart attacks. Our superoxide dismutase, derived from mitochondria, just couldn't resolve some of the key aspects of re-perfusion injury, as in strokes, because the half-life in the blood was too short. High enough blood levels could not be maintained sufficiently for an adequate period of time. It is still an important problem, and no doubt this problem will be approached via other SOD's.

Hughes: Put simplistically, Genentech and other early companies had the idea that you clone the gene and you have a drug. What came very soon to be realized was, you've got to know a lot about the biology.

Rutter: Yes, to some extent we all suffered from that simple notion and the hubris that came with it. But that idea didn't die very soon. It came after a decade of failures. That's why it was such a big lesson and why virtually all the companies suffered a challenging period. Success did not come the easy way. The hubris of which I speak existed in most of the major biotech companies of that era. There were strong individuals who weren't used to failing.

Hughes: You include Genentech?

Rutter: I think so.

Hughes: Why?

Rutter: Because many of the original products did fail or had limited success.

Hughes: You are thinking of the original projects which came from UCSF?

Rutter: That is another matter. I was thinking of the products which have made Genentech arguably the strongest company in the field today. They are projects that were co-developed with others in the last few years, and I think that was due to the wisdom of current Genentech management, which is superb, perhaps with the advice of Roche. [Fritz] Gerber especially, I believe, and some of the others at Roche helped shape Genentech and limit its scope, focusing on cancer. Art Levinson has done a fabulous job in building Genentech. In that focusing, they wisely were not restricted to their own technology but collaborated with others, and in so doing succeeded famously. So that was a case where a big company and a little company really complemented each other well. Of course, Amgen was extraordinarily

fortunate in two products, which are the leading products in the industry. They've had a succession of successes after good management in the early years by George Rathmann.

Hughes: To interpret simplistically, what you're saying is that a lot of Genentech's strength came from its relationships with Roche, and Amgen's success was somewhat based on luck, that they had research projects that paid off quickly and well.

Rutter: No, I wouldn't ever say that. And I didn't mean it. I meant to say that the relationship between Genentech and Roche seemed complementary, a good balance, at least it seems so from the outside. It wasn't Roche that really provided the leadership; they provided sage advice to complement the strong people, and I think they showed the wisdom to choose Art Levinson and support him. Earlier, Bob Swanson without a doubt was an extremely strong leader.

Hughes: A hard question: Chiron was founded almost at the beginning of the biotech revolution. Why didn't it have the blockbusters that Amgen and Genentech had?

Rutter: Well, I think our major contributions were the hepatitis B vaccine which in some ways was a blockbuster product in the context of its effect on world health, although it didn't bring huge sales to us. I think the discovery of hepatitis C represents a milestone not only in the industry but in biological science. That resulted in the Lasker Award [for Clinical Research, 2000] for the team who were immediately involved in the project. If it had occurred in an academic setting, it might have received the Nobel Prize. Further, that discovery plus the development of the viral-load measurements directly support the research which has led fifteen or twenty years later to the development of HCV drugs against hepatitis C. The sequencing of HIV and its quantitative measurement similarly added to the ability to protect the blood supply and enabled Gilead [Sciences] and others to develop small-molecule therapeutics which now save the lives of tens of millions of infected people worldwide. These discoveries and developments represent blockbuster science and also blockbuster business, in my view. The business surrounding the HIV, HCV, and HBV diagnostics, and the purification of the world's blood supply, and the concept of viral load—these are blockbusters. Bottom-line revenues from these contributions I think match some of the contributions made by the other companies.

However, the continuing success in the diagnostic arena was blunted by the decision of Dr. [Daniel] Vasella [Chairman and CEO, Novartis] to not allow the merger with Roche Diagnostics and eventually to sell the business in favor of generation of cash as opposed to building the business. There was also the unfortunate decision to delay and eventually not acquire Gen-Probe, which was crucial to the nucleic acid testing for HIV, HCV, HBV. Instead of

committing to the strong businesses Chiron had, the new management elected to build the therapeutic business and unfortunately was unable to do so in a decisive fashion. The challenge was how to use those resources generated by the sale of Diagnostics and of Chiron Ophthalmics to build new businesses. At that time, there was a significant effect of the change of control that was fundamentally caused by the Ciba-Geigy/Novartis partial acquisition, which resulted in a fundamental shift in the business strategy—to small-molecule drugs.

HCV was a blockbuster both in terms of the science and opening up of the field and in its effect on the diagnostic business. Quantitative tests for HIV, HCV, and HBV changed the diagnostic industry and the blood-products industry. So in terms of the effects on numbers of human beings, I think we did okay. Unfortunately, Chiron didn't consolidate its position by decisively building on that base.

We had a strategy to work on fields rather than just on products. In building business around fields, we had that opportunity. The needed resources came in part with the Ciba deal, but the merger of Ciba and Novartis and the change in management and change in strategic focus of the company led eventually to the acquisition by Novartis. and left the Chiron strategy as unfinished business.

Hughes: What was your thinking in deciding which fields to work on?

Rutter: Well, it came from the philosophy that new strategic information coupled with novel technology and the related intellectual property can change a whole field, to the benefit of society and to the company developing or controlling it. That was true in the critical new proprietary products in diagnostics, and it was true in vaccines where recombinant techniques showed that biological mimicry can yield lasting protection without the possibility of causing the disease it is designed to eliminate. And then also the use of growth and developmental factors, the compounds that really influence the dynamics of the living system, we thought would change medicine, and new information regarding biological mechanisms would also lead to the best biological products. We were looking for biological products. In many of the specific programs, we were in races with the other organizations, for example on factor VIII. On balance from when we started, I think we did okay.

[Tape 13, Side A]

Hughes: Burr, Egan, Deleage & Co didn't have as close a relationship with Chiron as Kleiner Perkins had with Genentech?

Rutter: We had an excellent relationship with Jean Deleage but little interactions with Craig Burr or Bill Egan. It was an initial investment, and we did not have a

continuing relationship. Certainly they did not promote us like Tom Perkins did Genentech. But again, we did okay.

Hughes: Was your approach to the public derived from your experience in academic science where scientists generally base their statements on the facts—prove to me, don't tell me. It's a different attitude than when you're promoting your company in investment circles where there's a lot of bluster and not necessarily substance.

Rutter: Well, there are different strategies in academics, too, and I don't believe that it's a good idea to say our approach is a big reflection on that. I think it has more to do with my own personality and probably Ed's as well. There are great people in business who don't self-promote, and there are other people who promote all the time.

The whole biotechnology industry has been reliant on public interest and excitement about the potential products. As everyone knows, the industry has required a lot more investment from the public market than the public was getting out of it in term of stock price. You probably remember the *Wall Street Journal* article on the financial balance sheet of the biotech industry where after twenty-five years there was a net loss of nearly $50 billion. It took a huge amount of investment, essentially underwritten by the market, but it is changing rapidly and will go positive soon. On the other hand, the net effect on medicine and people's lives is, I contend, distinctly positive.

[interruption]

Hughes: Towards the end of 1990, maybe into 1991, there was an important event in Chiron history, namely the acquisition of Cetus. Could you tell me the background and the rationale for a substantial acquisition?

Rutter: This was the first major example of industry consolidation. Cetus was just next door to us and had the misfortune of having a major disapproval from the FDA concerning their product, IL-2 [Interleukin-2]. Bob Fildes was their CEO and virtually bet the company on it. When this happened, the stock price went down dramatically and confidence in Fildes as the CEO was eroded also dramatically. The board had to do something, and we recognized by virtue of its proximity it was an interesting opportunity to contemplate. But also we recognized that Cetus by virtue of its size, the amount of money it had on its balance sheet, its position in the marketplace, and the dimensions of its research program, (which was outstanding on the therapeutic side), that it represented an ideal opportunity for us to create a merged company that could truly operate more effectively in the tripartite mode. So we began having delicate conversations—

Hughes: With Fildes?

Rutter: No, not with Fildes. With the chairman, Ron Cape, and eventually with the board members. The person who was the greatest help in putting it together was Fred Frank, who saw the wisdom and the practical issues, particularly the financial impediments, Fred contacted Roche, particularly its chairman Fritz Gerber (with whom he had interacted in the Roche/Genentech purchase), to sell the royalty rights for PCR. This facilitated a transaction that was acceptable to both parties. Because of the differences in history, size of the companies, we decided not to treat it as an acquisition but as a merger. We attempted merge the two companies and give adequate consideration to Cetus perspectives. I think that was due to our attitude in general that building consensus and having an open society was the best way to develop a thriving organization. (After all, that had worked for us). On the other hand, Cetus, it appeared, was a rather structured top down organization, with an already well established, culture.

Hughes: That authority originated with Fildes?

Rutter: No, with Ron Cape, who was chairman. Fildes was the CEO, and the person immediately in charge of running the organization.

Hughes: You feel Cape had a strong hand on the company?

Rutter: Historically yes, of course, but at that time it seemed, Ron had delegated operational roles, including strategy to Fildes. However Ron was still the chairman and ultimately responsible to the shareholders.

Hughes: But originally Cape had a strong hand?

Rutter: Originally, yes. Ron Cape and—

Hughes: Peter Farley.

Rutter: It seemed that Peter Farley had a very strong operational and strategic role.

Hughes: Explain a little more. They were the ones in control? It was not a consensus organization?

Rutter: They certainly controlled the organization. I can’t comment on the extent to which there was consensus and how they worked at it. But for sure, it was an organization which was, at the time we knew it, more typical of structured organizations with delegated individuals who had the authority to make decisions. It was not an open society. So for years after the merger there were the Cetus guys and there were the Chiron guys, who would identify themselves as such. “I’m a Cetus person, and this is the way we do it.” They had many very good people within the organization, along with the culture of the past. We tried to retain Hollings Renton, who was appointed president of Chiron, while Ed was of course the CEO. We also tried to retain the good

research people, particularly Frank McCormick, who was essentially their chief scientist. But it became clear that they wished to form another company, and eventually we agreed to the formation of Onyx. Onyx was not a spin-off in the usual sense; it was a recognition by us of a fact of life, that those individuals wanted to start their own program—besides Hollings, Bill Gerber, the person who was head of Diagnostics for us, and Frank McCormick, who was responsible for the oncology research program in Onyx.

Hughes: These were all Cetus people?

Rutter: All Cetus people. All of these people left and this program was emasculated. But still Chiron had all the intellectual property that resulted from this acquisition; had the problems of dealing with IL-2 and interferon beta. So on the commercial side, we were assiduously working on a way to maximize the yield from those and redeveloping a program to get approval of IL-2, which we succeeded in doing. It just took an immense amount of energy to shore up the business side. At the same time, the key scientists were, well, thinking in other directions.

Hughes: What did they take with them to Onyx?

Rutter: Well, they took, narrowly, a set of projects which were oriented toward cancer and which had been conceived and led by the chief scientist McCormick. Sam Collela, from Versamt, a premier venture capital organization, saw an opportunity to recruit this scientist, who was an excellent person in the field along with the program he led. They awarded him a large bonus of shares (or options and therefore upside), something as a member of our group we could not provide. All that Cetus personnel converted their options in the acquisition, so he got a bonus of money. So did Hollings. So did Bill Gerber. Then afterwards they came in within the Chiron organization, and they had to start all over again. So at that time a venture organization could come in and offer another package to the employees, which, if successful, would bring them lots more money along with the independence which is attractive in a separate small company in which they become the key management. A very attractive opportunity. So the acquisition, by its very nature, had within it an incentive for key people to leave, and that's what happened.

So, we had to be realistic. They were going to leave somehow. We negotiated for them to take some of the projects which we couldn't have realistically carried on without them, So we came to an accommodation and took a relatively small share of Onyx, and that was it. The share was enough so that in principle had we wanted to buy back later, we could have done so, and that would have been all right, too, with Sam Colella. The immediate consequence, however, was it began to erode some of the purposes and the future of the biopharma division. Anyway, that's the kind of thing that was, in hindsight, to be expected. Maybe we should have facilitated it. In hindsight, we learned a lot about acquisitions. Mergers of equals rarely if ever work.

They are, or become mergers of unequals. One must assert leadership and control early in order to achieve a common culture.

There seems to be no single solution when two distinct cultures are brought together. I am told that in Ciba-Geigy, thirty years after the merger of the two companies, the personnel still identified themselves as a “Ciba” man or a “Geigy” man. So cultures have a tendency to persist, just like familial relationships do, because there are strong relationships between people and ideas and programs. Nevertheless, if you work at it and are assiduous about it, the people who don’t buy into it leave, and the people who do buy into it stay, and therefore you can have some kind of coherence. That’s what’s demanded. It’s not possible to have an organization with too many cultures and expect that the individuals in the organization will rapidly adapt to the new culture and work together,

Nevertheless, there was a richness within Cetus not in the products but within their research. They had a wonderful immunology program. They were farsighted early. That program consisted of making monoclonals against many targets, and among them had been a monoclonal against HER-2 for a breast cancer product later. There were diverse projects and we didn’t and couldn’t take advantage of them all. Many were in very early stages of development but were quite major in their requirements for future development. But we were doing other things, too, trying to build businesses. Lack of focus but also lack of real understanding of each of the programs and having somebody to really push it forward was an issue for us. If we hadn’t been able to do it ourselves, they might have been valued by somebody else. That might have been a potential spin-off which would have enabled the value to be unlocked.

Hughes: I don’t see how Chiron could have missed those opportunities. My knowledge of Cetus after Fildes comes in as CEO is that it was an immunological company, or at least immunology was a large part of their research base.

Rutter: None of these products were product candidates. There was a lot of information, a lot of patents filed, but when we bought Cetus, there were two products.

Hughes: Betaseron and—

Rutter: Yes, and Interleukin-2. That was it. Then there were some research projects, and some of them were elegant, but they were technological approaches, they really didn’t evolve into a product. Well, we carried forward one product on septic shock that had come from that program.

Hughes: Well, then, what were you buying? Were you buying Betaseron and IL-2?

Rutter: Yes, we were buying Betaseron, IL-2, the whole organization, which had infrastructure that we didn’t have, and we were buying this research portfolio.

We did look over the research portfolio. The analysis was carried out quite broadly. The monoclonal approach, which evolved in the late nineties as opposed to ten years before that, we didn't have the personnel or the resources to initiate a major program in that field (which it needed). Further, our position in the field of immunology wasn't strong enough to drive the company in that direction. We looked at all programs that were suggested internally, or by our advisors.

Hughes: Cetus had an amazing advisory board.

Rutter: They certainly did, including people like Francis Crick. We talked to a number of the key people, Stanley Cohen, in particular.

Hughes: Did he join the Chiron board?

Rutter: No, he was with Cetus Immune, a group located near Stanford. He talked to us, but it was a question of finding a program which we could work together on, and we weren't big on scientific advisory boards at the time. We were more focused on programs. Of course, we were involved in immunology, too. The vaccine program is an immunology program. Several of our projects were antibody projects. It was a question of selecting the most attractive programs and planning out their execution. The TNF program was an internal program. It didn't come from Cetus. I consider that our biggest miss. So it wasn't that we simply dismissed Cetus projects. We looked at them. A company could have been built around monoclonal antibodies perhaps, but it would take a lot of resources, and time. We were certainly not in possession of exclusionary IP.

Hughes: Yes, right. I know that Don Glaser was on the Chiron board for seven years. Were there others from the old Cetus board who joined the Chiron board?

Rutter: Yes, several.

Hughes: Did you find them helpful?

Rutter: Don, of course, is an extraordinarily intelligent and constructive person at a high level, so he was superb in discussions, but perhaps not so valuable in discussing operational details. We had others that were primarily commercial-type people in different fields. Carl Djerassi was on the board. Obviously, he is also an extremely bright and experienced person, but I think he was also oriented more to his own personal take on projects, he had been involved with in Cetus' past, rather than the current pragmatic interests of the company. It was a somewhat awkward period. We never heard any strong opposition or strong suggestions by the Cetus group and after an appropriate period of time board we began to transition toward a more functional board. We lost some individuals from both companies, but eventually ended with a smaller functional board.

[Tape 13, Side B]

Rutter: The Cetus discussion emphasized one of the fundamental areas of emphasis and strengths of Chiron, which was the belief that intellectual property would shape the future. We were one of the companies, after Genentech, that developed an internal intellectual property group, an extremely strong one. Although Genentech had arguably the most driving IP attorney—

Hughes: Tom Kiley.

Rutter: Tom Kiley. We had Bob Blackburn, one of the most sophisticated and overall intelligent practitioners in the entire industry. This proved itself in the areas of our strength, especially in hepatitis C and HIV, but in many other areas as well. After the acquisition of Cetus, we used to show slides where the numbers of patents we had in biotechnology would be roughly equivalent to that of major international corporations.

Hughes: I read that as of 1984—this is from the annual report—you had well over a hundred patents pending.

Rutter: Not surprising in 1984, but I would guess in five to seven or eight years after, we had more than a thousand. That number of patents created a challenge to management both from the standpoint of cost and also utility—the strategic management of the IP portfolio was a significant issue. It was a major balancing act to give the intellectual property portfolio the attention it deserved and the resources it needed.

Hughes: Who was primarily responsible for that kind of thing?

Rutter: Bob Blackburn was of course in charge of the patent estate.

Hughes: Yes, but he was a patent attorney. Was he also responsible for seeing that Chiron took advantage of its patent positions?

Rutter: No, that was a more broadly based set of responsibilities. Bill Green, our corporate attorney, had the responsibility of developing a strategy for protecting the IP from a strategic as well as practical point of view. Also, the director of research had a significant role. (Pablo Valenzuela, or later Rusty Williams). The number became so large, and the analysis of them became so specialized, that maximizing the value of those properties was always an issue. It always is an issue in a company that has a large intellectual property portfolio.

Of course we became involved in other internally generated projects too—ones where we made major contributions. The first one of which was AIDS, which started after hepatitis B, as a result of a collaboration with Professor Jay

Levy at UCSF. He had indications of a retrovirus, whose function at that time was not totally well known, but was associated with Kaposi's sarcoma patients. It turned out to be one of the initial clones of the HIV/AIDS virus. We decided, because of its size and because of its properties and its likely association with disease, that it was worthwhile tackling. So we established a program that aimed at culturing it in large enough levels to be able to sequence the genome. Essentially this became our next target.

Hughes: You make it sound so deliberate. I mean, there was a tremendous race at the time, as you are well aware.

Rutter: It had to be deliberate, because it required a lot of capital—human and financial. In the early days we were not sure it was the same virus.

Hughes: Oh, is that so?

Rutter: Yes, we were not assuming that it was the same virus, but soon it became obvious. And in any case, there was a race to sequence the next infectious agent that was transmissible and related to disease in humans.

Hughes: But were you assuming that it had a connection with the disease?

Rutter: Well, that was before AIDS was recognized as a disease. We were assuming it was related to Kaposi's sarcoma, and we were presuming that anything like that would have maybe had a broader disease manifestation. But in the early days, it was not recognized that it was going to be an international disease of the dimensions of AIDS.

Hughes: Because it's such an important part of history, say how Chiron's research with Jay Levy was related to the Robert Gallo-Luc Montagnier controversy over priority in discovering HIV.

Rutter: Well, we were working like crazy to sequence that virus, and somewhere along the line we realized it must be the same virus, or a closely related variant. It certainly was a race to get the required amount of material and then doing the sequencing. There were many heroes in that race, for sure. But I think Kathy Steimer (now deceased) was preeminent. She did all the culturing of the organism herself to provide material for sequencing. She didn't want others involved because of the danger. She was absolutely resolute, and we all owe her a debt of gratitude. The rate of progress of the project really depended on her. Of course there were other people who were involved in sequencing the virus who were absolutely extraordinary and dedicated all the way. Paul Luciw and Dino Dina were involved at that time. The people in the laboratory all working under Pablo were outstanding. No one is better than Pablo in directing the execution of a research program. I think there is little doubt that Chiron got the sequence first.

Hughes: What came out of that race was that Gallo's virus was actually Montagnier's virus.

Rutter: Well, that may be, but that had nothing to do with us. Our virus had an independent source. It was not Montagnier's virus.

Hughes: Well, it was indicative, though, that there were a variety of different AIDS viruses.

Rutter: Well, it was indicative. Yes, there were subtle variations. But did that mean there were only two? No, not necessarily. But the fact that there were different variants to the same virus only became clear when the sequences were compared.

Hughes: But the fact that the other people sequencing all came out with virtually identical sequences, except for the Chiron group, showed that it was very likely that the other groups were using the same virus, which was Montagnier's.

Rutter: Yes.

Hughes: Well, Chiron did have a role in showing that there were variants.

Rutter: Yes, for sure. But as far as our intellectual property on HIV was concerned, it contributed to our position with respect to discovery and a broad IP position. But that aspect was a sideshow. A major sideshow, but still a sideshow. These observations really fueled our enthusiasm for our overall strategy. Another important virus needed to be characterized so that it could be detected, quantitatively assayed, and hopefully eventually controlled, and we had the technical wherewithal to do it. That supported both the diagnostic and vaccine approach. We immediately began working on a diagnostic test and also a HIV vaccine. Here we are more than twenty years later, still no vaccine. But the quantitative tests for the virus have allowed elimination of major sources of viral spreading in the population, and also the ability to develop drugs, which have been spectacularly successful, especially in the hands of Gilead.

At the same time this was going on, we had a major research focus on hepatitis non-A, non-B, as it was called. There was evidence for infectious viral hepatitis that was neither hepatitis A or B (since both had been characterized they could be distinguished). We tried to find out whether there was one or more viruses causing non-A, non-B hepatitis. Of course it turned out to be a single virus which we termed hepatitis C. At this time, we were at the center of viral research working on two of the major viruses causing enormous public health problems. Because of their limited size, both could be characterized by sequence and hence could be studied quantitatively with the methods we were developing. Let me emphasize these were major whole-company projects, the entire management group was focused on the execution

of the projects. We had research meetings nearly every Saturday in which the detailed results were discussed and future experiments planned. Pablo was directly involved in planning and analysis of experiments, and I also participated in strategic planning, starting with negotiating with the CDC for the use of blood from infected chimpanzees which had been characterized by Dr. Daniel Bradley. One of the chimps, Rodney, contained virus in sufficient quantities so that it could be isolated and characterized. So it's not surprising, on the one hand, that we couldn't take on many other projects, and in the context of our focus on infectious disease, it was appropriate that we focus where we were focusing. We had support for vaccines, we had support for diagnostics within the context of these joint fifty-fifty deals we had previously negotiated. On the other hand, it created an issue: how were we going to develop therapeutics when so much effort was being devoted to getting FDA approvals of our diagnostic tests and getting some kind of commercial framework in which to further develop the organization.

About the same time, we had two other technology-based programs that emphasized both the scientific and the technical diversity and the problems of diversity within Chiron. One of them was Protos, which was a program that came out of conversations that Dan Santi and I had had, concerning the possibility of developing peptides as therapeutic agents. The general idea was that peptide libraries of sufficient complexity could readily be synthesized and screened for optimal binding, and usually drug targets (e.g. immunologic epitopes) were smaller and could be addressed by these peptides, either as quasi-epitopes or as direct binding to targets. Eventually patents that emanated from those conversations were filed. It was essentially a chemical approach, but it had a genetic flavor in the sense that one could ostensibly produce all the combinations of peptides, and those peptides then could act either as binders or target analogues (e.g., as epitopes). Diversity of that magnitude was an analogue of genetic diversity, yet it was addressable by chemical synthesis. So it was a strategy that might be linked to immunology as well as therapeutics. It was an interesting idea in the context of where the science was at that time, and where we were as a technology company. So we set up Protos as a separate company, mostly because of the strong desire of Dan Santi.

Hughes: Did he want to be a Chiron employee?

Rutter: No.

Hughes: Was he coming straight from academia, straight from UCSF?

Rutter: Yes, but he retained his position at UCSF. He participated part time. Protos eventually ended up with twenty-five or thirty people. It developed intellectual property, had a separate option plan, and a formal relationship with Chiron. The consequence of that was that the employees inevitably wanted to get the best of both companies. They preferred equity (options)

from Chiron when it was doing well and independently from Protos when they thought Protos might be doing better as a startup. The two companies were independent though Protos was wholly owned. We spent a lot of time negotiating and haggling. It became contentious at times and very difficult to manage in a fashion that satisfied both groups.

Hughes: Why did you have to work together?

Rutter: They were getting their resources from Chiron, and there was not an easy way to get resources elsewhere for them, and so it was just a constant haggle. In the end we decided we had to repurchase their shares at a negotiated price established by attorneys. There are great difficulties whenever that sort of thing arises.

Hughes: So what happened in the end?

Rutter: We bought back the shares at an aggressive price in order to resolve the issue.

Hughes: Was that the end of Protos?

Rutter: That was the end of Protos and the beginning of a program with peptide chemistry/biology.

There was this Australian company, Commonwealth Serum Laboratories in Melbourne, that also had a program called Mimotopes, that was based on the same general principle: a synthetic approach to peptides, essentially solid-phase synthesis on a pin that could then be used for discovery and analysis. It was a very nice idea pioneered by Mario Geysen. CSL wanted to spin out Mimotopes since it was not related to their general interests in vaccines and blood products. Because of its close conceptual relationship to Protos we were attracted by it, and eventually we purchased it, and it became an adjunct, largely research business on its own. It was an excellent research tool. We used it to define the epitopes of hepatitis C, for example. We tried to develop it as a research business. It was too far afield from Chiron's interests and strengths to maintain as a separate research business within Chiron.

Hughes: So is that another example of being too widely oriented?

Rutter: In one sense, absolutely. However at that time the research on proteins, and specifically antibodies, was technology-restricted by the available tools. It was very useful and potentially differentiating for our own research business to have avant garde techniques and approaches. So we attempted to add to the breadth of our research capabilities and in this case facilitate their use by others as well. This would help pay for the development of the technology, and we'd get the research benefit from it. It turned out to be partially successful. We did sell to the market but never reached the magnitude that would truly support the development of the technology. It was a distant

organization, so it represented a management challenge, so eventually we split it off.

Hughes: Does the company exist?

Rutter: It was eventually bought by MitoKor, a company that focused on mitochondria that Walter Moos started.

That company is now defunct, and Mimotopes was eventually incorporated in some form into Genzyme and also Pepscan. Mario Geysen, I believe, in some way became affiliated with these programs. Pepscan today is well known and widely used for epitope mapping.

Hughes: After Chiron had divested.

Rutter: Yes.

Hughes: [laughs] Let me check see my notes.

Rutter: You didn't do badly.

Hughes: And you did very well. One wind-up question about Chiron. If you had to name one thing that you did for the company, what would it be?

Rutter: I don't believe in such questions.

Hughes: But you'll answer it anyway, won't you?

Rutter: No, I don't think I will.

Hughes: Well, when you look back at Chiron—

Rutter: Well, Chiron is truly a reflection of not just my personality but my approach to both science and business. It's a coordinated approach which is based on an unfailing belief that technology can be applied to programs which benefit people. I'd say we established an extremely strong science base and, immodestly, well, we changed the diagnostic and vaccine industries, and I think that's an enduring change. I think research enterprises can wax and wane, but the persistence of those things, such as a strong science base, continues. And I think hepatitis B, hepatitis C, and the strategy of dealing with high technology for diagnostics will persist. I'd say intellectual property as a component of building a business is stronger in Chiron than in many other companies. I mean the relative contribution of patent revenues and using a research organization as a strong continuing base for revenues. Now, other companies are doing that nowadays, but I think our strategy was particularly evident in concept and in practice. Chiron contributed the view that size doesn't matter as much as concepts and the reality of what you have to offer,

given the right set of circumstances. Obviously, size does matter, but ambition and attitude and novelty match it. Okay.

Hughes: Okay. I thank you.

[End of interview]

CURRICULUM VITAE

WILLIAM J. RUTTER

Birthdate: August 28, 1927

Birthplace: Malad City, Idaho

EDUCATION

1946-1949	B.A.	Harvard University	Biochemistry
1949-1950	M.S.	Universitv of Utah	Biochemistry
1950-1952	Ph.D.	University of Illinois	Biochemistry

ACADEMIC AWARDS AND HONORS

1967	Pfizer Award in Enzyme Chemistry, American Chemical Society
1981-2	Faculty Research Award, UCSF
1983	J.J. Berzelius Award, Karolinska Institutet, Stockholm
1986	20th Brown-Hazen Award, State of New York, Department of Public Health
1986	Kroc Visiting Professor, Joslin Diabetes Center, Harvard University Cambridge,MA and University of Texas Health Science Center, Dallas
1987	Bertner Award, M.D. Anderson Hospital & Tumor Institute, Houston, TX
1993	Member, Fellowship of the International Institute of Biotechnology
1996	Honorary Doctor of Science, University of Illinois
1996	Honorary Professorship of Science, Eotvos University, Budapest
1996	Honorary Doctor of Science, Eotvos University, Budapest
1996	University of California, San Francisco Medal

ELECTED MEMBERSHIP ACADEMIES

1984	Member, National Academy of Sciences
1987	Member, American Academy of Arts and Sciences

1993	Fellow, American Academy of Microbiology
1992-98	Member, Harvard Board of Overseers
1998-	U.S. National Academy of Sciences Council
1998-	National Research Council Governing Board

BUSINESS AWARDS AND HONORS

1992	Ernst & Young and Inc. Magazine Northern California Entrepreneur of the Year Award
1993	BioPharm Achievement Award
1994	Harvard Business School Northern California Entrepreneur of the Year Award
1995	Heinz Award for Technology and the Economy
1998	Biotechnology Hall of Fame (Biotechnology CEO's)
1999	Jacob Heskel Gabbay Award in Biotechnology & Medicine
2000	The Bower Award for Business Leadership from the Franklin Institute
2003	Biotechnology Heritage Award
2004	Inductee to the Bay Area Council Hall of Fame

PROFESSIONAL POSITIONS

l963-l965	Professor, Division of Biochemistry, Department of Chemistry, University of Illinois, Urbana
1965-1968	Professor, Departments of Biochemistry & Genetics, University of Washington, Seattle
1968-1982	Chairman, Department of Biochemistry & Biophysics, University of California, San Francisco
1983-1989	Director, Hormone Research Institute, UCSF
1968-Date	Hertzstein Professor of Biochemistry, Department of Biochemistry & Biophysics, UCSF
1981-1999	Chairman of the Board, and co-Founder of Chiron Corporation, Emeryville, CA (resigned from board December 2003)
2001	Chairman Emeritus, and co-Founder of Chiron Corporation, Emeryville, CA
2002	Chairman/CEO, Synergenics LLC, San Francisco, CA

Consultantships

Abbott Laboratories, North Chicago, Illinois	1960-1975
Eli Lilly Co., Indianapolis, Indiana	1977-1980
Merck and Co., Rahway, New Jersey	1977-1981
Chiron Corporation, Emeryville, CA	2000-2003

Scientific Advisory Board

AMGEN, Newberry Park, CA	1979-1981

ACADEMIC (non-profit) INSTITUTIONS - *Board of Directors*

Harvard University Board of Overseers	1992-
Novartis (Ciba-Geigy) Board of Directors	1995-1999
Carnegie Institution of Washington	1995-
Board of Trustees	
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