Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Program in the History of the Biological Sciences and Biotechnology

Roberto Crea

DNA CHEMISTRY AT THE DAWN OF COMMERCIAL BIOTECHNOLOGY

Interviews Conducted by
Sally Smith Hughes, Ph.D.
in 2002

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

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Roberto Crea, 2003 *photo courtesy of Roberto Crea*

BIOTECHNOLOGY SERIES HISTORY--Sally Smith Hughes, Ph.D.

Genesis of the Program in the History of the Biological Sciences and Biotechnology

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

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

The Bancroft Library is the ideal location to carry out this historical endeavor. It offers the combination of experienced oral history and archival personnel and technical resources to execute a coordinated oral history and archival program. It has an established oral history series in the biological sciences, an archival division called the History of Science and Technology Program, and the expertise to develop comprehensive records management plans to safeguard the archives of individuals and businesses making significant contributions to molecular biology and biotechnology. It also has longstanding cooperative arrangements with UC San Francisco and Stanford University, the other research universities in the San Francisco Bay Area.

In April 1996, Daniel E. Koshland, Jr. provided seed money for a center at The Bancroft Library for historical research on the biological sciences and biotechnology. And then, in early 2001, the Program in the History of the Biological Sciences and Biotechnology was given great impetus by Genentech's major pledge to support documentation of the biotechnology industry.

Thanks to these generous gifts, the Bancroft has been building an integrated collection of research materials--oral history transcripts, personal papers, and archival collections--related to the history of the biological sciences and biotechnology in university and industry settings. A board composed of distinguished figures in academia and industry advises on the direction of the oral history and archival components. The Program's initial concentration is on the San Francisco Bay Area and northern California. But its ultimate aim is to document the growth of molecular biology as an independent field of the life sciences, and the subsequent revolution which established biotechnology as a key contribution of American science and industry.

Oral History Process

The oral history methodology used in this program is that of the Regional Oral History Office, founded in 1954 and producer of over 2,000 oral histories. The method consists of research in primary and secondary sources; systematic recorded interviews; transcription, light editing by the interviewer, and review and approval by the interviewee; library deposition of bound volumes of transcripts with table of contents, introduction, interview history, and index; cataloging in UC Berkeley and national online library

networks; and publicity through ROHO news releases and announcements in scientific, medical, and historical journals and newsletters and via the ROHO and UCSF Library Web pages.

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

Emerging Themes

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

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

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

Location of the Oral Histories

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

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

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

January 2004

ORAL HISTORIES ON BIOTECHNOLOGY

Program in the History of the Biological Sciences and Biotechnology
Regional Oral History Office, The Bancroft Library
University of California, Berkeley

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Oral histories in process:

Moshe Alafi
Brook Byers
Ronald Cape
Stanley N. Cohen
Donald Glaser
Irving Johnson
Daniel E. Koshland, Jr.
Lawrence Lasky
Arthur Levinson
Diane Pennica
George Rathmann
Steven Rosenberg
William J. Rutter, volume II
Axel Ullrich
Mickey Urdea
Pablo Valenzuela
Keith R. Yamamoto

INTERVIEW HISTORY--Roberto Crea

DNA synthesis capability are the three words which tersely explain Crea's trajectory from the University of Leiden to southern California and then on to Genentech in 1978. He was among the first scientists hired by Genentech as it opened its unprepossessing facility in South San Francisco. But Crea's connections with Genentech antedated his arrival by more than a year. He honed his expertise in the chemical synthesis of DNA at the City of Hope Medical Center, outside Los Angeles, in the laboratory of Keiichi Itakura, one of the few experts in this then arcane field. He became a member of the Genentech-supported UCSF-City of Hope team bent on demonstrating that bacteria could be engineered to produce proteins from non-indigenous sources. In 1977 the collaborators announced that they had induced bacteria to express the mammalian protein somatostatin. It was a spectacular proof-of-principle experiment that indicated the commercial potential of the new genetic technologies of recombinant DNA and DNA synthesis. From there the team went on to achieve a similar feat in the production of human insulin.

Crea tells in this oral history of his contribution to these early successes, the background and response to the somatostatin, insulin, and growth hormone work, his formation of a DNA synthesis group at Genentech, and considerably more. What Crea makes abundantly clear is the advantage that DNA synthesis capacity gave to Genentech at a time when no other company had the technology. He also suggests the gung-ho, highly competitive, youth culture of Genentech. The attitude to just about everything was, as Crea puts it: "Let's go for the Big Enchilada." But all was not sweetness and light. In 1981, wishing to stretch his own wings, Crea left Genentech and went on to found the first of several companies. He is today the founder and chairman of a company producing antioxidants from olive oil.

Oral History Process

Five interviews were conducted in Dr. Crea's office in Hayward, California, adjoining the plant which produces olive oil from which several products are derived. The company is one of three with which Crea is currently associated as founder. He spoke in fluent English stamped with the accent of southern Italy, land of his origins. He carefully reviewed the interview transcripts, at first making numerous changes which after the first chapter dropped to a minimum. By agreement with Genentech regarding the oral histories it supports, its legal department received transcripts of all interviews to review solely for current legal issues. As in all other instances to date, no changes were requested.

The Regional Oral History Office was established in 1954 to augment through tape-recorded memoirs the Library's materials on the history of California and the West. Copies of all the interviews are available for research use in The Bancroft Library and in the UCLA Department of Special collections. The office is under the direction of Richard Candida Smith, Director, and the administrative direction of Charles B. Faulhaber, James D. Hart Director of The Bancroft Library, University of California, Berkeley. The catalogue of th Regional Oral History Office and many online oral histories can be accessed at http://library.berkeley.edu/BANC/ROHO. Online

information about the Program in the History of the Biological Sciences and Biotechnology can be accessed at http://library.berkeley.edu/BANC/Biotech/.

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University of California, Berkeley
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INTERVIEW WITH ROBERTO CREA

[Interview 1: June 27, 2002] ##

Hughes: Dr. Crea, would you tell me a little about your family background, beginning with your grandparents on both sides?

Crea: I didn't have the fortune to meet my grandparents. When I was born, my grandparents, from my mother's side as well as my father's side, were dead. My grandparents from my mother's side both died by diabetes, a distance of one year. My grandfather, Bruno Milea, died first, and then exactly one year later, my grandmother, Caterina, died. I imagine that at that time diabetes was a disease which wasn't easily treated. I know a little bit of my grandfather from my mother's side, from what my mother told me and from my relatives. My grandfather was a businessman in Calabria, southern Italy. He was a very intelligent entrepreneurial person who had built a very strong position in the field of essential oils extraction (extraction of essential oils).

Calabria and many other regions of southern Italy are famous for their warm climate, almost like California. So, there are a lot of flowers and citruses. A hundred years ago there was a group of entrepreneurs who had started extracting the essential oil from the flowers of orange trees and lemon trees and other flowers like jasmine. They were selling the oil to cosmetic companies all over the world, including the United States. For instance, I learned that my grandfather came to the United States when my mother was still a young girl, for business reasons, which was very unusual because travel was so difficult. He had to travel by carriage from southern Italy to Rome, most likely by train from Rome to other European countries, and I'm sure that he traveled by cruise ship to the United States. I think some of my entrepreneurial skills come from that side of the family.

My mother, Giuseppina Milea, was the youngest of five kids—two boys and three girls. Her family, as I said, were fairly rich for people at that time. They had a lot of houses and land. Unfortunately, that didn't help her, because after the death of her parents, my grandparents, she was the last of five kids who were quite young and inexperienced in taking over a situation which hadn't been planned. As a matter of fact, the business side, the company and most of the real estate assets, went to the two brothers. At that time the law in Italy was such that in case of death of the head of the family, the assets would go to the boys. So my mother ended up with nothing. On top of that, she got married very young. My father, Francesco Crea, wasn't coming from a similarly rich family, so the two brothers didn't look at the marriage in a positive way. So my parents had to struggle to raise a family.

My mother passed away this past April, at eighty-six years old. My father is still alive, eighty-seven years old, and he has worked for his entire life in the railway business, as an employee of the state, Italian Railway. In retrospect, I understand that it wasn't easy for them to raise four kids and provide for all the necessary support for kids to go to school, which we all did. We went to elementary school, which at the time in Italy was five years. After, there were three years of intermediate school, and then there was high school for five additional years. All the kids in my family had the chance to attend schools.

I started school, as many other kids in the South, in a small village in Calabria where my father was working in a central electrical power station, providing the technical support for the trains to move around. That was his expertise. Then after the elementary school, as I started the intermediate school, my family moved from this small village in Calabria, called Scalea. They moved back to Reggio Calabria. We ended up living in a small village in the periphery of Reggio Calabria, which at that time was the capital of the Calabria region. We lived in the Gallico Marina, which was about five miles away from the city's downtown. I attended the intermediate school and high school in Reggio Calabria.

I finished my high school in 1968. I took the scientific direction. I attended a scientific lyceum rather than the classics lyceum. The classics lyceum is a high school where you study more of the classics field, like Latin, Greek. The scientific lyceum provides more of the scientific disciplines, like mathematics, physics, some focus on elemental biology.

Hughes: Why did you go in the scientific direction?

Crea: I felt that I was more inclined to science than classic studies. I particularly enjoyed mathematics and the logics behind the scientific disciplines. My sister chose the classics. She then became a teacher of Latin and Greek languages in high school. I didn't want to do that. I was the last of four kids—two brothers and one sister, then me. I was the youngest of the family and as such I enjoyed more freedom than the rest of my siblings. My early interest was for mechanical engineering, and I never thought that I would become a chemist. I always wanted as a child to build boats and ships. My ideal of a career was to become an engineer for building big boats.

Hughes: What were your parents saying about these ambitions?

Crea: Well, they were obviously listening to me, although they were more preoccupied to see me doing well in early school, which I was doing.

Hughes: Were you the student of the family?

Crea: My sister and I were essentially the most brilliant of the family. My first brother never really managed to accomplish a brilliant academic career. My second brother stopped going to school after getting a diploma as a technical engineer. It's a low degree, but it allows people to start working in some sort of trade.

Hughes: Would that be the counterpart of a vocational high school degree?

Crea: Yes. So, my sister and I were the only two kids to pursue university studies. My sister got a doctoral degree in human sciences, and I ended up studying chemistry. That came later. My dream was to finish high school in Calabria and then to move to northern Italy, in Piedmonte, in Turin, where there is one of the best engineering schools. The reason I was hoping to get to Turin was that I had an uncle who moved with his family to Turin many years earlier, so I had a place to go. Obviously, I was hoping to minimize the cost of moving from my family to go study in a different place.

Hughes: So there wasn't a lot of money for your education?

Crea: Well, for the education up to high school I attended public schools. We were paying tuition every year. But in Italy, it's fairly accessible to everybody, so it wasn't until I started the university that the financial issue started becoming important. In a way, I managed to minimize the financial burden for my parents by getting the high school degree with a high score. That allowed me to apply for a grant in a university, which I obtained early on, so I was essentially supporting myself from day one. That grant would allow me to stay in the city where I was attending university, which was a city in Sicily just across the Strait of Messina. I was commuting every day, waking up early in the morning, catching a train to the place where the ferries would commute back and forth, go to the university to attend lessons, and in the late afternoon, catch a ferry and go back home. It was very tiring because I would get up early, like six o'clock, and come back eight o'clock in the evening, exhausted, and the day after I would do the same.

So, after a year or so of commuting, I found a boarding room in Sicily, near the University of Messina, and I was staying there five days a week. Then, Friday afternoon I would come back to my parents' house near Reggio Calabria and then start again the following Monday.

Hughes: Were you making friends?

Crea: Yes, a lot of friends. In Italy, especially in southern Italy, there's plenty of opportunity to socialize. We were finding ourselves together on the train, on a ferry, in the cafeteria of the university—so a lot of friends. Also, I was part of the Youth Catholic movement. Actually, since I was a kid I was educated Catholic, so I attended church. That has had an effect on me. I was also serving Mass when I was a kid, and I was part of the Catholic movement.

Hughes: What do you mean by "Catholic movement"?

Crea: Well, there is a church organization in Italy which favors the young groups who are interested in church affairs. It's called Azione Cattolica. It's like the Boy Scouts association, but less formal. We didn't have uniforms, but we belonged to an organized group of young Catholics. It was, among other things, an experience to meet friends, meet girls, play games. I became more involved as I grew up, because I started to attend national events. I became an educator of young kids. Educator means somebody like a mentor, somebody who can teach the Catechism, somebody who deals with young people's problems, coaches them in sports and in life, as well. So, I was very motivated at that time to learn more about the Catholic Church and the religion as well.

Hughes: Was your family religious?

Crea: Yes. Well, most Italian families are Catholics, although my father never professed himself as Catholic. The rest of the family pretty much followed a routine in Italy, where you go to church, you learn that you are born Catholic. If you find the right motivation, you start associating with other groups of people to learn more about the religion as well as create a style of life. It's a way of life, not different from other people's, but in the context of a Catholic association, you do certain things. You are supposed to go to Mass, you learn about the novelties in the doctrine, you dig into the religion and try to be a good Catholic.

Hughes: Do you consider yourself today to be a good Catholic?

Crea: No, I lost that drive long ago. In part it is because most of it was dictated by the social context. You feel part of a community. Once you leave your community, you end up living in a new environment where you don't know many people; you don't have friends of many years. You get busy doing other things. In my case, that strong interest which I had for religion transformed soon into a strong interest for science. Not that the two things cannot live together, but time was very limited, especially when I had to work hard in order to finish my degree.

Hughes: Did that transformation begin to happen when you were in university?

Crea: Yes, correct. It started as a gradual moving away from religion when I moved from University of Messina. It was 1970, so I was twenty-two years old. I moved to northern Italy to start my final university studies. That decision was mainly dictated by the desire to learn more about biochemistry and later on molecular biology. So, it was very much related to the studies I was attending. But in reality it put me in a situation where I lost most of the contacts with my community and friends. Then I had to struggle to survive on my own in a new environment.

To the extent that I was going back to Reggio and my family, I was always part of that community. Recently I went back to Calabria after many years for the funeral of my mother, and I saw very old friends. It wasn't much changed. It was the same spirit. I had dinner with my friend priests. As I said, I was very much involved in the Catholic movement. When I was young, I had the chance to meet a lot of priests and travel with them in Italy. At dinner, we remembered the good old times when we were going to summer camps and educating kids. I felt I had lost in all these past years the opportunity to be an active Catholic. But the spirit of friendship and respect and love for one another has not changed, and that is part of the way you grow up and the way you get educated.

Hughes: Before we leave your first family, tell me a little about the quality of family life. Did you spend a lot of time together?

Crea: Well, as I said, my family was a modest family in that we were all depending on my father's salary as a railway worker. But it was a family that grew up with a lot of dignity. We were what you would call middle class. We used to live in one apartment, which was provided by the state railway company. There were sixteen apartments in two buildings, so there were lots of opportunities to familiarize with other kids from a similar family situation. I never felt any discrimination based on my family. On the contrary, I spent most of my early youth in a serene environment in a village where the economy was pretty much linked to jobs belonging to a state railway.

So, my early years were spent in a family which in part was struggling financially; we were living in the postwar years. It wasn't until the sixties that families of the middle class in Italy started getting more of a financial benefit. But until then, we were struggling. My mother was trying to dress us well, feed us well, but never in excess of course. We were sharing. We were aware of the financial situation of the family, but we were still finding plenty of times to be happy with other kids, playing with our co-eds downstairs in the front yard of the building, playing soccer, or running in the wild in the little hills surrounding the building. There was plenty of opportunity for very happy years with no conflicts of any sort, other than the feelings of an overall modest financial situation.

Hughes: Were you close to your brothers and sisters?

Crea: I was closer to my sister, Palma. She was the third. The difference between myself and my sister is only three years, while my two brothers are kind of different generation. They were living growing pains much earlier than I was, in terms of meeting girls and hanging out with the co-eds. So, for me, being the youngest in the family, it was more enjoying the freedom, because I had fewer responsibilities than the other brothers. But sometimes I was always getting the short end of the stick—in terms of allowances, for instance. I was getting enough to go to the movie on Saturday and that was it. I had a little money to buy myself ice cream when I was going to school, but the rest was up to my mother to manage the financial situation. I never complained.

Perhaps I learned early on that the lack of financial means in the family can create conflicts, and there were conflicts between my older brother and my father. Very often I would witness quarreling back and forth about how we were spending money and the need of saving. For the young of us, it was normal; we didn't have any other yardstick, any other comparison, so we did the best we could. I didn't particularly enjoy being mistreated by my older brother, sometimes being told to do the dirty jobs, having to obey and shut up just because I was the little one. Other than that, I spent a lot of my free time outside the family. Not that we were not close to each other, but each one was too busy going to school during the day. When we came back from school, everybody was going in his or her direction. I was going to see my friends and playing with them.

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Crea: Sometimes my parents couldn't afford to buy new shoes. Sometimes you had to wear your older brother's clothes. Things like that, but other than that we were living well in that small village in southern Italy. Watching television for us was magic, maybe not in my house, because we couldn't afford it until I was adolescent. But to go next door to another family with a television and watch the early programs, sometimes things that were coming from the United States like Rin Tin Tin in black and white, was fascinating.

Hughes: Well, once you got to Messina, you started a course in chemistry. Why chemistry?

Crea: I was ready to move from Reggio Calabria to Turin when I finished my high school. But in the summer following my graduation, my uncle died by a freak accident. He was in the police, and somehow he got killed by gunshot. We never knew whether it was an accident or more than that. It was a trauma for everybody to lose my uncle. For me, it was out of the question to move away from the family under those circumstances. So, I was kind of disoriented. My father, as often, came up with a beautiful suggestion, which I accepted because I didn't have any real alternative. My father suggested that I start chemistry at the University of Messina because chemists were in high demand by the industry at that time, and I could most likely get a job at the end of the university.

Hughes: Chemistry, as opposed to engineering?

Crea: As opposed to engineering. There was no good engineering school in Messina. Chemistry was a very good faculty. To be honest with you, I didn't know what chemistry was all about when I started, but I accepted it as kind of "This is my destiny. Now let's start." I don't want to lose any time. So, I went to Messina and enrolled myself and started

chemistry the following fall. That was really a big trauma for me, not only because I had to commute—it wasn't easy to commute—but also I didn't quite understand anything about chemical reactions. It was a completely brand-new world. I had never done anything at high school to be prepared for the lessons and the learning that I was going through, so it was really very hard. As a result, the first two tests that I took were mediocre. The first score was twenty-one out of thirty, and the second one was eighteen out of thirty, which was the bare minimum. Of course, I thought that the professor had been unfair, because I had worked very hard to learn as much as I could.

In general, I can say that the first three years of the university weren't happy ones, besides being away from my friends, my family, my first girlfriend, as well. I had a lot of troubles seeing myself in the laboratory, concocting reactions with bad smell and long hours, things that didn't mean that much to me. So it was like, okay, if I had to do this, let's do it. I'll try to do my best. But there was no passion to what I was doing.

Hughes: What about the chemistry faculty?

Crea: The faculty was a good one. There were some good professors and some bad professors. Probably the first year in chemistry, there were about one hundred students attending lessons. It was clear the second year and the third year, the number had to be dropped dramatically. It was a tough faculty. The degree in chemistry was considered to be one of the most difficult ones. There were thirty different exams in order to go through. In Italy, as you know, the university is different from here in that it is a mix between Ph.D. and master degrees. You do almost a Ph.D., because at the end of the studies you write a thesis and do experimental work. So, it was like a grim perspective, and that grim perspective was in part compensated by the fact that I met new friends in Messina. It was a new world, more independence. It was part of the growing-up process. It was a heart-shaking experience in that I was very insecure, vulnerable. Financially I wasn't well taken care of. I had this responsibility to do well, because I couldn't fail and create an additional burden to my family. I wanted to do well, because my idea was, well, if chemistry was all there is, I might as well finish as fast as I can and move on.

And then something suddenly happened in the third year of university: I enjoyed very much attending biochemistry. Biochemistry was for me almost a miracle. It was not only because finally I was learning something interesting about living organisms, but also a great professor was teaching biochemistry. That professor, Mr. Giovanni Cuzzocrea, was a fantastic teacher, a gentleman, and a visionary. So, I fell in love with biochemistry. Finally there was something that I really could develop a passion for.

Unfortunately, that faculty had only one or two courses related to biochemistry, so it was clear early on that I had to look somewhere else, other than Messina, to continue learning and building my knowledge in biochemistry. So, what I did after I passed the test, of course, with maximum scores—thirty plus laude, thirty is the maximum score, plus the laude which is an extra reward, I asked my professor to drive me in this decision-making process to continue my career in biochemistry. Professor Giovanni Cuzzocrea told me that I had to leave Messina if I really wanted to do more. That wasn't surprising to me; I had already made that decision myself. I remember he gave me three letters. He said, "During the summer break, why don't you take a week or two and go visit these three friends of mine who are heads of laboratories in northern Italy and talk with them. They

might decide to accept you in their laboratory, in which case you will continue in biochemistry and maybe you can also write a thesis in biochemistry."

That is exactly what occurred. In 1970, I visited two of the three and the second one, Prof. Alessandro Castellani, was in Pavia. He was so interested in my desire to do more in biochemistry that he offered me an internship in his laboratory. So, I finished the remaining exams in Messina very quickly because I wanted to finish all the third year tests and then go to Pavia.

I moved to Pavia in the fall of 1970, and I start attending the laboratory of Professor Castellani. He was the head of the biological chemistry department in the University of Pavia, which is a prestigious university in Italy. It's located near Milan and is one of the oldest medical schools and universities. It was formed by Cardinal Borromeo and the church in the late eighteenth century. So it had a great tradition. I realized when I went to Pavia that it was almost like being in Cambridge, England. It was a lot of bright people, living in colleges, like in Oxford. It was really an intellectual elite as compared to southern Italy.

Hughes: Had you passed entrance exams? How had you gotten in there?

Crea: Well, no. There was a lucky circumstance. The year I decide to move was also the year where the Ministry of Scientific Affairs of Italy had introduced a new law which in essence allowed students to move freely from one university to another.

Hughes: Do you know the circumstances for that law?

Crea: Well, they wanted to make it easier for students to learn from different universities. They introduced the concept of "Piano di studio," a plan for your academic career. If your plan was acceptable to another university, in theory, you could move and start studying there. Again, let's not forget that universities in Italy still are state institutions. They are not private institutions, so it was easier to move from one university to another. So, I had my piano di studio and I presented it to Professor Castellani and the faculty. I have been very grateful to Professor Castellani for accommodating my aspirations by letting me work in his laboratory. I finished the course in chemistry in Pavia by taking the exams of the fourth and fifth year without a glitch. I also worked on my experimental thesis, and I graduated with a doctoral degree in chemistry in 1972.

I did very well in Pavia. It was strange for me. It was my first experience in the laboratory, but I did very well because I had a very intelligent teacher, a supervisor, who ultimately ended up taking over Professor Castellani's position. His name is Cesare Balduini. Professor Balduini directed me toward very interesting research. I was working on cartilage metabolism and cartilage diseases. Early on, I was cracking eggs with newborn chicks, and in a very tedious fashion I would pull out one by one the tibias, which is the leg's long bone, out of these little creatures and put them in ice. When I had collected enough, maybe a couple of grams, I would homogenize these little bones. I would crush them in a blender to create a homogeneous collagen suspension, and that was my starting material.

As we got more sophisticated, instead of going in the morning to fetch fertilized eggs, I would go for newborn pigs, which was a little more gruesome. I would go to the farm

and get two or three newborn piglets, bring them back to the laboratory. The poor creatures would be anesthetized and killed. Then, I would remove some of the bones and scratched the thin layer of cartilage between them. That was my starting material for the experimental studies needed for my thesis. After a few weeks, I learnt how to cope with this unpleasant situation. The research work was fairly interesting and successful because as I studied the enzymatic components of the cartilage at an early stage, we found some new enzymatic activities.

Hughes: That was unexpected?

Crea: Yes. I managed to develop a new method for the fractionation of the various intracellular components of the cartilage. I was one of the few students in Italy capable of isolating the rough reticulum from the smooth reticulum from the plasma membrane from cartilage cells. So, we had really developed an interesting fractionation of the cartilage into components, and we could study now the enzymatic activity associated with the different membrane components. It was fascinating to me. I did write my doctoral thesis on this. I also used the experimental data of my work to prepare my first oral presentation at my first scientific symposium in Italy, which was kind of unique because I wasn't even graduated when I spoke at the symposium. So, obviously I was talented enough for Professors Castellani and Balduini to keep me involved with the laboratory, because there was competition by more qualified students coming from Pavia's prestigious colleges.

That was the work I did for my thesis, which I presented the day of the graduation and discussed it the way they do in other European universities and here in the U.S. for the Ph.D. degree. I got a very high score. I graduated with one hundred and seven out of one hundred and ten. I would have achieved the maximum if I didn't have the early bad scores from Messina. So, I paid for that. But in the end not only I managed to graduate, but also I managed to stay involved with the laboratory of Professor Castellani because they appreciated my laboratory skills and my way of thinking creatively.

Hughes: Do you consider yourself to be good technically with your hands?

Crea: Yes, very good. Later on, a famous professor in Holland described me as the chemist with golden hands. [laughs]. So, I think I'm pretty good experimentally.

Hughes: Did you have any idea from any past experiences that you would be a good experimentalist?

Crea: No. I had no idea that I was going be very comfortable with my hands. Also I found myself intrigued in learning what other people were doing. Everything was some sort of discovery. In high school and university you're used to studying books. You have to memorize a lot of things and then you have to answer the questions when you take the test. I remember one of the toughest exams was organic chemistry. We had to study from five books, including the famous U.S. book, Boyd and Boyd, which was a thick book, five inches of chemical reaction. You had to memorize everything because you couldn't miss anything for your exam. Then, when you take the test and the professor says, "Write the reaction between this chemical and—whatever," you have to remember that reaction. So, I was glad to move from memory to experiments in Pavia. I was happy to set up experiments, and I was pretty good, I guess, designing the right experimental condition to generate useful information.

Hughes: Who decided that cartilage would be your research topic?

Crea: It was Professor Castellani, who had trained in Chicago in early years. This laboratory in the U.S. was focused on cartilage and disease of cartilage. It was very important field because the University of Pavia has a very strong medical school and many collaborative projects with hospitals. Some of my more senior colleagues in Pavia were working together with M.D.'s and clinicians at the hospitals to understand the pathology underlying cartilage diseases. So there really was a medical component which made our research more interesting and focused.

I was pretty happy in Pavia, although the weather was miserable. It is a city where you have fog six months a year and humidity the remaining six, with a lot of mosquitoes in the summer. [tape interruption]

Hughes: When did your interest in molecular biology emerge?

Crea: When I was still involved with the laboratory of Professor Castellani at the University of Pavia, after graduation, I was interested in learning more about new areas of science. My interests coincided with the fact that the science faculties, of which my biological chemistry department was a part, decided to establish a three-year post-graduation course, like a Ph.D., although there was no Ph.D. title per se. Part of this specialty three-year course was the study of molecular biology.

I was extremely fortunate to meet a professor who was back from the United States, from Cleveland. His name is Professor Francesco Campagnari. Professor Campagnari was a really bright scientist, very passionate about research. He was one of the professors who was going to teach the specialty course. I enrolled immediately and started attending lectures held by Professor Campagnari, and next I found myself extremely interested in the new concept of DNA, polymerase, gene replications. Campagnari had a background in biochemistry, and he had several years of experience in Cleveland, at the Case Western University, studying the replication of DNA. At that time that was the big novelty coming from the United States, especially from Stanford and the work of Arthur Kornberg. It was really intriguing to learn the enzymatic mechanisms responsible for the duplication of DNA, but also for the formation of messenger RNA. It was really exciting to learn the most intimate cellular mechanisms. So, I jumped on this immediately.

Hughes: Was that your first exposure?

Crea: It was my first exposure to learning about the enzymes involved in DNA replication.

Hughes: How unique was that course?

Crea: It was very unique. It was the first in Italy. It was just the first year that they had started, so I was there at the right time.

Hughes: That would have been 1973?

Crea: Correct. I really established a good relationship with Professor Campagnari, because I was helping him produce transparencies, pictures out of books and other teaching material. I was almost his right arm. He really appreciated my enthusiasm. Professor

Campagnari had his own laboratory in a little town called Ispra, near Varese, which was a European laboratory. It was called Euratom.

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Crea: While I was involved in the laboratory of Professor Castellani, I had managed to get a grant from a prestigious organization, called the Academy of Linceii. It's an old Italian scientific association. They were paying me about 1.2 million liras a year, which was the equivalent of about a few hundred dollars a month. With that salary I had to pay for the apartment, transportation, and live on it. As a matter of fact, during the first years of postgraduate work in Pavia, I was the only graduate waiter at a very popular dancing pub just outside the city. I was trying to survive, believe me, and I didn't want to ask my family for financial support.

I remember an episode which I never forgot: one day I parked my car in the wrong place, and they gave me a ticket which was a third of my salary. In that case, I had to call my family and say, "Help me, because this month, I'm not going to make it." It was tough. I was a young graduate student trying to fit into an academic system which was very competitive with other graduate students, perhaps with more credentials than mine. So, I was doing okay and never complained.

When I met Professor Campagnari, however, I talked to him about my precarious situation with the University of Pavia—I was an assistant professor, in effect. I asked him if he had a job in his laboratory group in Ispra. Professor Campagnari really wanted to give me a job in his lab, but he didn't have any opening. He suggested a couple of things, which ultimately turned out to be crucial for my career. He suggested that as I was waiting for a position in his group I should apply for a research grant with the European Community and try to spend a couple of years in other European laboratories where I could learn some techniques which eventually would be useful to his laboratory and his research at Ispra. When I asked Professor Campagnari, if he could suggest such laboratories in Europe, he said, "Let me tell you. There are two laboratories where I would go if I were in your shoes. One is in Paris and the other is in Leiden, Holland. The one in Paris, you learn more of the molecular biology techniques and the DNA enzymology. In Holland, you learn more of the DNA chemistry." For me it was, "Well, I don't have any way to decide. What would you suggest?"

He said, "The group in Holland is very innovative. They're doing something that is extremely important and novel, because they are synthesizing DNA fragments, small pieces of DNA, by chemical means. They are doing it under the leadership of this young professor, Jacques Van Boom, who is a rising star in Europe. I would go there, because you are a chemist and your background is in chemistry. If you learn how to synthesize these molecules, then we have a better chance to learn how these enzymes work." It was a perfect, logical, rational presentation!

So, I agreed with him. I said, "Maybe I'll go to Holland and learn DNA chemistry, and we'll write together a scientific plan, so that I can produce some molecules that you can use in your laboratory. When you are ready, I'll come back to work for you at Ispra." We made the first request to one of the scientific agencies of the European Community, called EMBO, the European Molecular Biology Organization, which is one of the major European organizations that sponsor inter-country studies. So we made a request for me

to go to Leiden, and we got a quick rejection. It said, "Unfortunately, we don't have any money available at the moment, so you have to wait." That was 1973. The second year, I continued in Pavia, with the hope that I would get this grant. If I remember well, I finally got a telegram from the European Community which was confirming my request had been accepted and that I had to get ready to go on short notice. That was December, 1973.

I remember I got the good news while I was spending some time with my parents in Calabria, because it was Christmas. When I got that telegram I was extremely excited. My parents weren't so excited because I was going to Holland away from them. But, once more, they were happy for me that I was moving ahead with my career. It was going to be one year or maybe two years and then I would come back to Italy.

And that was the beginning of my career outside of Italy. The grant was from January 1, 1974 to the end of December, 1974. I remember Professor Campagnari said, "Well, one thing I don't like in this"—I said, "What, Professor?" "Well, you are going to make a lot more money than you do right now, and I'm afraid that you are going to get spoiled." The European Commission has to pay good salaries in accordance to the European standard. I said, "Well, that's a good problem to have, especially after two years of misery." So, I loaded everything I had in one small car, a Citroen which they used to call "the Duck," which I had purchased in Pavia, and I took off for new frontiers.

Hughes: Had you been out of Italy?

Crea: Never. It was fascinating. I was driving, by myself, this overloaded car, over the Alps. I was driving this poor ugly car, probably at forty-five miles an hour, with all those big trucks behind me when I crossed Austria. It was beautiful in the late morning. Then I got into Germany, which was a terrible experience. The freeways in Germany are crowded with a lot of traffic. By then, I was in the first true adventure of my life. After twelve hours of driving, I ended up stopping in Ulm, Germany, to see my brother who had found a job in Germany. I spent the night at my brother's apartment and the day after I left to drive all the way to Leiden. I got to Leiden in the early afternoon on a sunny Saturday, and I stopped my car next to the open market, along a canal. I grabbed a fish sandwich from a vendor, and to me it was like, "Woo! This is incredible." Everything was new—the atmosphere, the architecture, the colors, the flowers, the fish, the canals. It was the beginning of an incredible adventure. There was only one big problem—my English was lousy. I never studied English in school.

Hughes: And neither did you speak Dutch.

Crea: No Dutch. I had learned my broken English out of books the last year in Pavia. I had literally written on a piece of paper my introductory speech for Professor Van Boom, and I remember when I first showed up at the Gorlaeus Laboratory in Leiden, I had a piece of paper in my hand. I had written my few sentences like, "Professor, thank you very much. My name is— I am happy to be here." Professor Van Boom was a young guy, in his early forties, with a lot of energy and enthusiasm. He had just come back from England where he had learned this new chemistry, called phospotriester method, in Professor Colin Reese's laboratory, at Kings' College in London—chemistry that was being applied to work in DNA synthesis. Jack was setting up his own group in Leiden. He must been positively affected by my naivete, because he said, "Okay, that's good. Tomorrow I'll ask

one of my Ph.D. students to take you through the research we are doing here in my lab." I was happy that I had survived that first meeting.

The day after I had one of the most interesting experiences in my career. I got together with one of the students, Peter Van Deursen, who was doing the Ph.D. thesis in Dr. Van Boom's laboratory. We sat down in a little room, and he said to me, "Roberto, let's start from the beginning." I said, "Okay, Peter, go ahead." He said, "Well, first of all, you have to know that carbon can form four bonds with other atoms." It was like, "Wait, Peter. I might speak bad English, but I have five-plus years in chemistry. We don't have to go that far back!" That fortunately lasted only a few days, then I started working in the lab and establishing myself. By the second year, I was totally doing my things and I was also coming up with my ideas. The first year was more focused on executing the plan that Professor Campagnari and I had put together, and I was pretty successful in doing that.

Hughes: That was to make the enzymes?

Crea: No, that was to create some substrates for the DNA enzymes.

Hughes: DNA substrates?

Crea: DNA substrates. So, the first work was to create a poly-dT [deoxythymidine] attached to cellulose, because the poly-dT would have been used as a substrate for isolation of messenger RNA or to create some junction between DNA strands for the characterization of ligases, enzymes that fill gaps. That was my first work, and I think that was the first time that I used the cellulose to immobilize DNA.

Hughes: Was the lab using it?

Crea: No, they weren't using it. I was linking chemically-activated mononucleotides to the cellulose, and then I would add more dT for making dimers and trimers. So the work involved making chemically synthesized dimers and trimers on a solid support with a dT, which was the easiest way, because dT doesn't involve blocking the molecule for possible side reactions. Once I attached those molecules to the cellulose, I had to quantitate the amount of dT immobilized on cellulose, and then use that derivatized cellulose to link other DNA substrates by hybridization and enzymatic ligation.

Hughes: Were other people in the laboratory doing similar work?

Crea: No. I was the only one, and in a way I enjoyed working in my own field. But I was learning from other people how to synthesize small pieces of DNA.

Hughes: Who else were there?

Crea: There were at least another dozen people. Three senior students, Peter Burgers, Peter Van Deursen, and Jan de Roy were getting ready to get their Ph.D. degree. They were working on their theses and were bright people. Dr. Burgers ended up working in biochemistry at Washington University, St. Louis. He is a well-established scientist. Peter Van Deursen ended up working for a large chemical company in Holland. Then there was a technician, Gary, a lady, working for Jack Van Boom. Jack was working at the bench himself, on and off, because he was teaching courses in organic chemistry. Then we had students who

would do practice in the laboratory and help us in building basic molecules or some reagents.

Hughes: Wasn't Herb Heyneker somehow associated?

Crea: No. Herb Heyneker was working in a similar laboratory, but in molecular biology at the Silvius Laboratory. Mine was the organic chemistry department. I joined the organic chemistry group at the Gorlaeus Laboratory.

Hughes: Did you mix much with other units?

Crea: No. We were working on the fifth floor of the Gorlaeus, and Van Boom's group was mainly involved in DNA chemistry, although they were also doing some peptide chemistry, as well. When I got there, that was it—a dozen people in the lab and Jack himself, and we were cooking and cranking new molecules. So, after the first year, I submitted my technical report to the EMBO commission and they gave me another year. The second year I was in Leiden, I continued working on the project of Professor Campagnari. I remember also I traveled to Ispra to give an oral report on what I was doing in Holland. I also gave a little seminar on the phospotriester chemistry, and then I came back to Holland to work on more challenging projects.

I got involved in one project where we were trying to add phosphate moities on the nucleosides, because the nucleotide di- and triphosphates would allow enzymes to use the molecules, in this case called nucleotide di- and triphoshate, to assemble along other molecules. Adding phosphate to nucleosides was important, because most of the energy in the cell is represented by ATP. ATP is adenosine triphosphate. So, the ability to chemically synthesize this energy-rich substrate would have given us a model to play with the enzymes and understand their mechanisms. To succeed in this project I had to find the perfect system to attach phosphates to the nucleoside. In other words, I would start with a naked nucleoside or protected nucleoside, depending upon which are the four bases I would use as substrate, and then I would add a phosphorylating agent to attach a first phosphate to the five-prime end of sugar, and then use that use that phosphate as a target for further addition of one or two more phosphates.

To make a long story short, my first publications in Holland relate to two areas. One is the synthesis of small DNA molecules, and the second one is the synthesis of monophosphate, diphosphate, and triphosphate via an active intermediate. This experience turned out to be very important for my contribution to gene synthesis at City of Hope and Genentech, in California, and we'll get to that. So, as you see here [indicates bibliography], my contribution in Leiden led to a paper which was submitted in 1975 by Professor Van Boom and myself as the second author. The title tells you that we were taking a single nucleoside and turning it into mono-, di-, and triphosphate.

In the meantime, Dr. Van Boom was gaining a reputation. He was getting on the international radar screen as one of the most creative and innovative chemists, and of course his group as well. He had a feature article in a chemistry magazine in Holland where people were talking about DNA and RNA synthesis and the possibility of creating genes as well. In reality, we were working with small synthetic molecules called oligonucleotides. In the meantime, Jack's group had published another paper where we describe the synthesis of an oligonucleotide of seven units, via the chemical coupling of

one nucleoside to the next and to the next and so on. There was no doubt in my mind that Jack Van Boom was one of the most creative leaders in oligonucleotide synthesis, and his reputation was gradually increasing due to the quality of his publications and the development of new methods.

Hughes: Were you urged to publish as soon as possible? Was there pressure?

Crea: Yes. Keep in mind that Professor Van Boom published, on average, between ten to fifteen papers a year. That was a lot for 1975. I managed to get two publications in 1975, and a lot of work wasn't published because the EMBO fellowship ended at the end of 1975. Jack managed to convince the University of Leiden to keep me in his lab as an associate professor. The university gave me a contract, through the ZWO research organization, to stay at the university as an employee, as an associate professor, to continue the work on DNA. They were paying me quite a bit of money for that time and I was supposed to do research for the benefit of the university. As the grant from the European Community expired, this new contract by the University of Leiden kicked in, so I had a third year to look forward, which was now 1976.

I enjoyed working as an associate professor in Jack Van Boom's laboratory. My duties were limited to do research in the area of DNA chemistry.

Hughes: Most people start out as an assistant professor. How had Van Boom managed to finesse—

Crea: Because I had already a Doctoral degree in chemistry from Pavia University, I first worked as assistant professor when I got the grant from the European community. So the fact that I had two years of assistant professor experience qualified me to be hired as an associate professor by the University of Leiden.

I enjoyed the period in Holland very much. For me, it represented almost a brainwash in terms of attitude toward research and freedom to be creative, freedom to express yourself, and for the quality of scientific research. Holland, with respect to Italy, was like day and night.

Hughes: Explain a little more, what the day and night was.

Crea: Well, in Italy, with all the financial constraint of a public university, you had very much a specific set of laboratory operations to do. You would be given some kind of assignment by your supervisor, but most of the time this meant the reproduction of other people's data. Somebody in the United States or England had published a paper with some intriguing results. If the Italian scientists wanted to learn more, they would try to reproduce that research in the lab. There was very little or no creativity or originality, at least for young scientists. For me, it was difficult to get excited about it. In addition, there was an overlaying philosophy in research which basically was "You wait until it is your turn. No matter how good you are, don't forget there are other people ahead of you in gaining job stability." Everything is so precarious in Italy that to get a job at the university, you have to wait six years, ten years. I was in an environment in Pavia where first of all there were other people before me. Second, there were college graduates with a college pedigree and much more prestigious academic credentials. I was in line for what and how long? For becoming an associate professor with no real autonomy, with no

freedom to pursue your own ideas. I was very happy to leave that environment, which was depressing in many aspects because there was no future for young scientists.

Hughes: Were you very aware of it in Italy, or did it take going to Leiden—?

Crea: No, I was not aware of it when I went to Pavia. Once I start realizing the uncertainty of the academic career in Italy, I got interested in doing something different. I didn't want to pursue an academic career, politics never appealed to me. I wanted to really learn how good research gets done. I think the experience of Prof. Campagnari in the U.S. and my experience in Holland made an incredible impact upon myself, because I saw the truth.

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Crea: In Leiden we were exploring, in effect, uncharted territory. What is fascinating and exciting in research is knowing that the work you are doing is done for the first time and that you can find new things that nobody has discovered before, and that you can learn some new concepts and new mechanisms. In the field of DNA chemistry, we all knew that Van Boom's lab was one of the world leaders, and that the better we were performing, the better chance we had to get recognized in the international arena. And then the environment was beautiful: first-class laboratory, modern building, modern equipment, no major constraints on purchasing chemicals, and reagents. In Holland, for instance, I was one of the few people in the world with the chance to learn to use an HPLC [high performance liquid chromatographer] for the purification of synthetic DNA. That also became very important when I joined City of Hope and Genentech. I was experimenting with a piece of sophisticated equipment which was a sort of prototype in the scientific world. I was gaining early experience in an area which turned to be very important for the gene synthesis from synthetic DNA fragments.

Hughes: How much interchange were you having with Van Boom?

Crea: A lot. I was working in the same laboratory where Professor Van Boom had his desk, and I had my bench space just across his desk. It was a wing of a laboratory floor, with one small lab in one corner connected to one big lab, and then a few more labs across the corridor. I was in the small lab together with Jack Van Boom and his assistant, so I had a chance to interact a lot with him, on a scientific and personal basis. We became good friends. Today, we are friendlier than ever, because of the many shared past experiences. Of course we have mutual respect for the things that we have done in our career. Our friendship goes back to the first two years I spent in Holland. He had a young daughter, Stella and a lovely wife, Lisbeth [Bep], and I was spending time with Jack's family a day or two every week at his place. When I was in the lab, I leveraged on my cooking skills and my Italian heritage to gain acceptance in the laboratory. So from time to time, I would give Italian parties in my apartment, full of pasta and meatballs, and everybody would come and go crazy on food, because in Holland the local cuisine is not the forte of that country.

It was a very enjoyable academic environment. I was playing soccer during the lunch break with other colleagues. I was one of the few Italians in a university building with more than a few hundred people. Little by little, I felt very comfortable, because the environment was so friendly.

Hughes: Was your English improving?

Crea: Oh yes. Of course, I was practicing my English every day in the lab. I was learning from television, radio. I even attempted to learn Dutch, but it was too overwhelming. Dutch has strange sounds that are not very compatible with Italian.

Hughes: Was English the language of the laboratory?

Crea: English and Dutch. It was almost fifty-fifty. I wouldn't understand the Dutch entirely, but I learned how to understand the most important things. English was my way to express myself and to communicate with other people. In Holland, English is the second language. Also, I found some nice people in the academic environment who loved Italy and were speaking Italian. Also, I met other Italian scientists in other departments of the university. Holland is a very open country, very liberal. Leiden University is one of the most prestigious, the university where Einstein taught physics for a few years, and is the first non-Catholic university in Europe. It's very liberal. They had also an Italian literature faculty, so I had friends there.

After three and a half years in Leiden, I was ready to leave, though, for many reasons. One, the contract with the university had expired. It was a two-year appointment, and at the beginning of 1977 I found myself living on social security. Financially, it wasn't bad at all because I was receiving eighty percent of my salary, but that wasn't a permanent solution. I had no chance to go back to Italy either because nobody in Italy was working in that area of synthetic DNA research. [tape interruption]

I was ready to go, because it was difficult to find a permanent job, especially for an Italian at the University of Leiden with my language limitation. But I was also getting a little bit tired of routine; things were looking kind of the same year after year. Holland is a small country, and after a while you can almost anticipate what's going to happen the next week and the next month. During my free time, I enjoyed very much visiting museums, a lot of art, music. I think those were very important years for opening my intellectual, scientific horizons and also socially and culturally.

One of the people I met in Leiden was Professor Arthur Rosch. Professor Rosch was a very important professor at the University of Leiden. He also was Herb Heyneker's boss. Professor Rosch knew Professor Campagnari very well. I must say Professor Rosch and his wife helped me quite a bit in the early time while I was in Holland, because Professor Rosch's wife, Thrus, spoke Italian. She was very nice in showing me around, helping me to find an apartment.

Professor Rosch was a very influential person in the University of Leiden in that he was the head of the molecular biology program. So through Professor Rosch, I met Herb Heyneker, and I learned more about Rosch's activity and Herb's work. I was still working in Leiden when Herb Heyneker moved to the United States to work with Herb Boyer. That connection was very important, because when Robert A. Swanson and Keiichi Itakura decided to recruit someone from Jack Van Boom's laboratory, they asked Professor Rosch and Herb Heyneker to check me out. It was Professor Rosch who, in response to the due diligence request, wrote to Herb that I was the chemist with golden hands. That was my reputation in the chemistry department of Leiden University. I still

keep a copy of his letter, so everything I am saying has a nice piece of written testimony that we can use to double check everything.

In the summer of 1976, Jack Van Boom got a letter from Dr. Itakura, indicating that there were postdoc openings in his lab. Professor Van Boom asked both Peter Burgers, who in the meantime had finished his Ph.D., and myself whether we were interested in going to California. I remember Peter Burgers rejected the offer, thank God!, to come to work for Itakura and Genentech.

Hughes: Do you know why?

Crea: It think he was little bit more conservative. He knew that as a Dutch scientist with a Ph.D. degree, he could have found easily himself a job in Europe or in Holland. So, he had more chances to get other jobs and he decided to step back and see what other offers were coming his way.

The letter from City of Hope and Genentech was pretty vague. Nobody knew of Genentech. Nobody in Jack's lab knew of City of Hope. Of course we knew of Dr. Itakura as one of the chemists involved in the synthesis of DNA from his publications while working in Canada. Professor Van Boom's reaction was, "Well, if you're interested, I'm going to write a letter to Bob Swanson, asking him to pay for a trip, because I want to go see for myself what's going on there." So, it was a way for Van Boom that he wouldn't miss anything new. But at the same time, it was to reassure me that I was going to work for a decent organization. Jack Van Boom traveled to San Francisco where he met Swanson. Then, Bob and Jack traveled together to City of Hope where they met Keiichi Itakura. Jack, after he returned to Leiden, told me of this trip and of his discussion with both Dr. Itakura and Bob Swanson on gene synthesis and the cloning strategy with synthetic DNA for production of proteins in bacteria. So, for me, after being reassured by Jack on the novelty and importance of the project, it was like, "Okay, now let's get ready for the big jump." After back-and-forth correspondence with Keiichi Itakura and Swanson, we finally decided that the best for me would be to join the City of Hope group under the Professor Itakura's leadership, starting in May 1, 1977.

So, that was, for me, the conclusion of an important experience in Holland and the beginning of a new one in the United States. I had no idea what was on the other side of the Atlantic. It was just too taken by this excitement to fulfill a dream of mine to work in the United States, especially in California. A young scientist, a European scientist, thinks of California as the dream country for many things, including research. I literally packed everything in two suitcases because I couldn't afford to bring anything else with me. I gave my furniture away to friends and put some in storage and, of course, I forgot everything about it. I left the Netherlands with two suitcases, an overcoat, and a brand-new camera.

May 1, I flew from Amsterdam to Los Angeles on a Boeing 747. It was pouring rain in Holland, and when I got Los Angeles, it was like ninety-five degrees. I was carrying my suitcase with my coat on, and people were looking at me as if I was crazy. My first impression of the United States and California—sunny sky, exotic palms, hot weather, the Lakers playing end of season games, the buses were striking, and I had to go from the Los Angeles International Airport all the way to City of Hope. I didn't know where it was, but I knew it was far away and that the taxi ride was costing me a lot of money.

Hughes: There you were. All right, we'll continue the story next time.

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[Interview 2: July 19, 2002] ##

Hughes: Dr. Crea, last time we brought you up to your arrival at City of Hope, so I think we should start today with your impressions.

Crea: The day of my arrival, I really didn't have any idea of what to expect in terms of work plan. I knew how to recognize Dr. Keiichi Itakura because I had a picture of him with me, but I never met him before. I didn't know much about City of Hope Medical Center either, other than that it was a major research center and a medical institution dedicated to treat patients with terminal disease, so from a scientific point of view, really it was kind of the beginning of a discovery process for me.

I asked the cab driver to drive me from the airport, Los Angeles International, to the City of Hope, and the reaction of the cab driver was, "It's far away." I said, "Well, I have to be there because tomorrow morning I start working, so take me anyhow." That cab ride cost me a fortune. It was almost a hundred dollars. But in any event, I got to the City of Hope at about 9:30 p.m. It was already dark, and I managed to get some information from a lady at the reception, and they were expecting me. She indicated that I would stay in one of the little houses they had on the campus, an area called Rosenkrantz Campus which had small apartment complexes for guests, just a room and a bathroom. I was happy to get into my room and crash after a long trip.

I remember in the morning I had an early appointment. Dr. Itakura was coming to pick me up at the apartment at the Rosenkrantz. I was ready for him with my blue jacket and tie. Suddenly I saw a fellow walking from the other side of the building in jeans and a striped tee-shirt, youngish looking, and I didn't know who it was. He came to me and said, "Hi, I'm Professor Itakura. Nice to meet you." So that was the first shock. I was expecting a more formal Japanese professor. But here was this guy—my age probably, dark hair, young looking, taking me to the laboratory.

Hughes: And speaking good English?

Crea: Speaking decent English, which made me feel better because obviously I was a little bit afraid of being able to communicate with my Dutch English. But that wasn't a problem. The first day I remember he took me to the laboratory, and that was kind of a surprise, too, because the laboratory was really a small one. It was a wing of the City of Hope Hospital. In essence, there were two rooms, plus a little office. The rooms were set up to accommodate a chemistry laboratory, with fume hoods and benches. But it wasn't more than a thousand square feet of lab space, so fairly small. I didn't dislike the idea of a small lab because the whole thing had the feeling of a totally new adventure. I had left a big building in Netherlands, seven floors, all laboratories, with all kind of sophisticated equipment. I was joining a California group, and it was all new and all exciting.

One of the first things that Dr. Itakura showed me was like a box, sitting on top of a table. "You see, we just bought an HPLC, and that's your baby. We were waiting for you because we understand you have experience with this kind of instrumentation." Then, the first day, he introduced me to some of the scientists—very few. There was one more Japanese postdoc, Dr. Tadaaki Hirose, and there was another Chinese fellow, a Chinese

lady, and a Filipino technician. That was about the size of the team. Then on and off a couple of girls came to the lab to wash the glassware.

He showed me the bench, and we spent some time going through the chemistry, the problems, the challenge. Dr. Itakura went on to explain what he was trying to do, the relationship with Genentech, the relationship with Bob Swanson and Herb Boyer, et cetera. It was great because not even twenty-four hours since I arrived in California, I was already comfortable in my scientific territory. I had my white coat, and I was ready to go.

Hughes: Now, had you heard about the arrangement with Genentech, before you arrived?

Crea: No, not really, and if I did, I wasn't paying too much attention. My perception before and after my arrival was that Genentech was sponsoring research at City of Hope, and essentially everything that we were going to do was in support of this collaboration between City of Hope and Genentech. All the chemicals, all the equipment, all the consumables, including my salary and other people's salaries, in the Keiichi Itakura laboratory were paid by Genentech. My understanding, which was confirmed later on by the hospital administration, was that I was to be employed by City of Hope as a City of Hope postdoctoral fellow, but in reality my salary with many other things was coming from a grant from Genentech.

Hughes: Had you heard about recombinant DNA? Was the name Herb Boyer familiar before you arrived?

Crea: Yes. Although I never met Herb Boyer before, he was just a big name in my mind, a big professor. I had seen some of his publications. I didn't understand well his research, because his field was totally different from what I had been trained. But I understood that the collaboration between the two organizations involved the City of Hope team to synthesize genes for mammalian proteins. Those genes were going to be used by the molecular biologists up in San Francisco and by Boyer's group at UCSF to create copies through the new techniques of plasmid cloning, and eventually to use the gene as a blueprint for production of proteins in bacteria. It was all new to me. Recombinant DNA had progressed in the U.S. to the point where things were happening almost on a daily basis. My focus, when I joined the Genentech team, was entirely on the chemistry. The big challenge was to synthesize oligonucleotides that could be used for the assembly of a synthetic gene.

Hughes: The somatostatin experiment had started.

Crea: Yes, absolutely. What I was told by Dr. Itakura when I arrived was that they were working at City of Hope to synthesize the gene for a fourteen-amino-acid mammalian protein called somatostatin. But things were slow because one or more of the fragments necessary for the assembly of the gene weren't working very well. There was a chance that we had to re-synthesize some of these fragments. They were also hoping that my experience in the purification of oligonucleotides by HPLC would be of help.

Hughes: Was your experience with HPLC one of the reasons that you were attractive to Itakura?

Crea: Well, I never asked him, to be honest, but I understood from day one that he was aware that I had experience with HPLC. A few years later, when I spoke to Professor Van Boom

about this issue, he confirmed that during his visit to Genentech and City of Hope, and during the phone discussion he had earlier with Swanson and Itakura, the issue of the purification of oligonucleotides was very important to Genentech because they were having problems isolating the pure material with traditional methods. They were indeed looking forward to purchasing an HPLC, upon my Dutch boss's recommendation, as a means to solve the problem.

Hughes: What did you immediately set about doing?

Crea: I remember the first couple of weeks were pretty intense because on one side I was working on putting up HPLC, setting up purification. On the other side, I was acquainting myself with the chemistry Itakura's people were using for the DNA synthesis. At the same time, I was developing new ideas on how to solve some of the problems that I saw immediately in the laboratory as some limitation in the oligonucleotide chemistry. It is fair to say that I was the most experienced DNA chemist in the group, with the exception perhaps of Dr. Itakura, who was dividing his time between managing the administrative aspect of his laboratory and active participation in the laboratory work itself. Dr. Itakura, in my mind, from day one was supervising the group, administering the relationship with Genentech, and overseeing the technical operation and progress generated by four or five people in the lab.

Hughes: So, he wasn't at the bench at all?

Crea: Honestly, I saw him often coming in and out, checking, monitoring, discussing with scientists, then going back to his office. I understand now the challenge: I think as a manager of a scientific team, probably, he was more involved in administration and overall direction and success, and he didn't have the time or didn't have the desire to be a bench chemist any longer.

Hughes: Did that surprise you?

Crea: No, it didn't surprise me because I already saw this kind of managerial challenge in the Netherlands. My former boss, Professor Van Boom, although a fantastic bench chemist, as his group became bigger—he had also some teaching obligations—he wasn't spending time at the bench in the laboratory any longer. He wanted to do it. He is a very talented chemist, and he was doing from time to time his own experiments. But not anything with continuity, which is necessary because it is difficult to start experiments and then walk away because of other obligations.

For me at City of Hope it was different: up in the morning, go to the lab, put on my white coat and start working from eight o'clock to six o'clock, seven o'clock in the evening. That was my life, trying to enjoy the work in the laboratory—produce, perform, invent, develop, deliver. So, I was a good fit for Keiichi Itakura in a way, because he started relying upon my experience to run his group. I was the second in command, and soon I became responsible for the laboratory operations. Because of my past experience in Van Boom's lab, I was able to make immediate contributions to the Genentech-City of Hope's effort, to the point that only a few months after I arrived, I was considered an important contributor to the somatostatin project. That was very exciting and rewarding for me, because, although the somatostatin project started and was going on prior to my arrival, I was able to jump in and become a contributor—and a good one—with the introduction of

the new techniques, both as related to the synthesis as well as the purification of oligonucleotides.

Hughes: Itakura, from what I understand, is known for the triester approach. Is that indeed what he was using when you arrived?

Crea: Yes.

Hughes: How did that jibe with what you were doing in Leiden?

Crea: Itakura came to City of Hope from the laboratory of Professor Saran Narang, in Canada, who is one of the few pioneers of the phosphotriester method. So Itakura was doing phosphotriester chemistry at City of Hope. Phosphotriester is a general denomination of a chemistry which is used to build long sequences from individual nucleosides. So the units need to be assembled into a string, and the way you could assemble at that time, was either by phosphodiester or phosphotriester. The phosphotriester was the new method, developed originally in England by Professor Reese and Professor Van Boom.

In the United States and North America, there were a few laboratories active in this area. There was a lab run by Professor Robert Letsinger, for instance, in Chicago at Northwestern University and a lab run by Professor Narang in Canada. So, at that time, less than a dozen laboratories all over the world were developing this new technique. Phosphotriester means that you fuse one nucleoside to the next, via a chemical condensation step which gives you a neutral molecule. The phosophate, which is necessary for the link between two nucleosides, is fully protected. That allows you to work up the resulting molecule, the synthetic product, in a much easier environment, which is organic solvents rather than going through water-based purification with the phosphodiester method, which is the technique that was perfected by Professor Gobind Khorana at MIT. The phosphotriester method turned out to be much more efficient, much more clean and elegant. It was clear, however, that there was a lot of work to be done to optimize a new chemistry to the point that one can control and scale up the single steps involved in the phosphotriester to be able to synthesize DNA fragments for the assembly of long genes.

That was exactly what we did in the Netherlands. I and my colleagues in Leiden worked for a number of years, trying to optimize the synthesis of small molecules into bigger ones. One of the key chemicals to accomplish a good synthesis with nucleosides is this condensing agent called phosphochloridate. In Leiden I worked with the phosphochloridate coupling agent using a lot of combinations between different chemical groups. So, when I arrived at City of Hope and I learned the special combination that Keiichi Itakura was using for the synthesis. I immediately combined what I knew from my Dutch experience with what Keiichi Itakura had put in place at the City of Hope. By doing that, I developed a very important chemical reagent which made the synthesis of dimers and trimers very efficient and simple. This chemical, which is called 2-cyanoethyl 2,4dichlorophenyl phospochloridate, turned out to be the object of a patent application by Genentech in 1978. I believe that was really an important development because it became much faster and much easier to produce a very large quantity of building block molecules, dimers and trimers, which you could now mass produce, purify, and store them in the refrigerator for multiple use. Then, when we needed to build a DNA chain of fifteen nucleosides, it became easy to do it from the appropriate dimers and trimers. We

were the first to develop the concept of a library of building blocks because it became much easier to make those building blocks with the chemical modification that I introduced.

Hughes: Did you make that modification quickly after your arrival?

Crea: I probably did after a couple of weeks, because the synthesis and the coupling phospochloridate used by Dr. Itakura's laboratory wasn't effective enough. As the chemical coupling was very much incomplete so the yields weren't high. But more than anything else it was difficult to purify the end product from the starting units.

Hughes: I heard about an episode where Swanson came down, expecting the experiment to work, and it didn't.

Crea: I think I can provide some insight to your statement. There were some problems concerning the purity of the DNA oligonucleotides, which I believe we solved very quickly by using the HPLC. I think that for the somatostatin project we only used seven or eight DNA fragments, but I remember that there was one fragment in particular that was giving problems during the assembly of the gene. I think it was fifteen bases long.

Hughes: This was before you arrived?

Crea: Yes.

Hughes: Did the problem continue?

Crea: After I arrived we re-did the synthesis and purification by HPLC and that immediately worked. So the somatostatin gene was reassembled with this new cleaned-up fragment and used for the recombinant DNA experiment. Now, what you are referring to is the fact that the first time we tried to express somatostatin in *E.coli*, we didn't see or detect any protein, and that was a big headache. I remember a meeting where we all convened to discuss the problem.

Hughes: Was Swanson present?

Crea: Yes, and Boyer together with Drs. Heyneker, Bolivar, Riggs, Itakura, and myself. Ultimately, out of that meeting an important discovery was conceived, which is the strategy of producing a small protein as a fusion protein in bacteria. In our case, this strategy consisted of putting the little gene for somatostatin (14 amino acids) behind the beta-galactosidase gene of *E. coli* (a much larger protein), and putting between the two genes a codon which in the bacterial cell produces an amino acid, methionine, which ultimately can be cleaved at the end of the process by treatment with a chemical called cyanogen bromide to release the somatostatin from its large, stable precursor. That, as far as I remember, was a contribution which was ultimately attributed to Professor Riggs. It was an interesting meeting because, as I remember, that was the first time the whole group convened at City of Hope—it must have been in the summer of 1977—to discuss the project and the experimental results. It was the first time I met Professor Boyer and Dr. Francisco Bolivar.

Hughes: It was the first time that you met Swanson?

Crea: Yes, it was probably the first time that I met Swanson. I remember that I had a brand-new camera from Holland, and I started taking pictures of the scientists walking through the laboratory and later discussing research results in the conference room. I think that in retrospect I took some of the first pictures testifying to the birth of biotechnology.

In retrospect, we had a year of extremely exciting events. We started with the failure to detect somatostatin as a product of the first recombinant DNA expression experiment. We came up with a scientific strategy that ultimately worked. And that led to the big announcement to the world that for the first time a peptide of mammalian nature, in this case a sheep protein, had been produced by bacteria. That was the first time Genentech and City of Hope sent out a big announcement via a press conference in Los Angeles, and I was a part of that together with Swanson, Boyer, Itakura, and Riggs.

Hughes: This is the first time I heard it was a sheep gene. I thought it was human.

Crea: No, we didn't have the human sequence; we had the sequence of a sheep protein.

Hughes: Which came from where?

Crea: From San Diego, from Dr. Vale.

Hughes: Oh, I wondered what his part was—Wiley Vale.

Crea: Wiley Vale was working on somatostatin. So the peptide was a sheep somatostatin, and we designed the gene. It wasn't a human. Insulin was the first human gene we used. So, for me, 1977 was like magic. I came from Europe to do my work. I can provide the DNA pieces. Other people will put together the pieces into genes and do the rest. I was happy to be a player, at that point.

Hughes: What was Hirose doing?

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Crea: He was doing similar chemistry, but the difference with Tadaaki Hirose was that he did not have any training in DNA chemistry. He was in Keiichi's laboratory for a postdoc experience. He came from Japan just to learn the synthetic DNA techniques. He was working at the bench doing in essence what Dr. Itakura would tell him to do, and then as we develop the new chemistry of coupling, he was involved in the synthesis of dimers and trimers using my improvements. He is a good chemist and a good, warm, intelligent person. He did not mind producing the building blocks and then assembling oligonucleotides—a very productive individual, very quiet, nice person.

Hughes: He spoke English?

Crea: He spoke broken English as many other foreign scientists.

Hughes: Tell me how the procedure went. Once you had synthesized the fragments, then what happened?

Crea: The first period at the City of Hope was taken by the somatostatin project as the major technical and scientific goal. That goal was meant to validate and satisfy the vision of Genentech's Boyer and Swanson. It was a goal for the City of Hope labs to establish ourselves as major partners of Genentech. It was a goal that turned out to be extremely important for the entire industry, because with the announcement of a successful expression of somatostatin, the world started taking notice that a bunch of scientists in San Francisco and City of Hope had done, for the first time, this kind of experiment.

I remember that it was a big event! We had a press conference at the Biltmore Hotel in downtown Los Angeles. In front of the press Robert Swanson and Herb Boyer announced to the world this event. I remember that the news was picked up by the media as a major scientific breakthrough. Also, at the same time, we heard that there was a testimony of the President of the National Academy of Sciences, Dr. Handler, before a recombinant DNA subcommission of the U.S. Senate which supported this event. Indeed, Dr. Phil Handler testified that this experiment was "a scientific triumph of the first order." It was maybe to my surprise, because I wasn't fully aware of what was going on—the thing was becoming bigger and bigger by the day.

From my standpoint, after the somatostatin fragments got out of the laboratory at City of Hope and became a project for the molecular biologists at UCSF, we were focused again on improving the synthetic chemistry. Out of that effort, which I can say that I led, we published two important papers describing the new chemistry to make the building blocks and the second describes the use of building blocks to make long DNA oligonucleotides.

I also remember two episodes. The first was the celebration with Bob Swanson in Pasadena. Pasadena has very good restaurants so we decided to spend an evening in celebration and to discuss future projects. I remember that after the somatostatin success, every time Swanson was coming to City of Hope, there was reason for celebration. I remember the celebration at this Italian restaurant. During that dinner, Bob raised the issue of the next project for the City of Hope group, specifically Itakura's group. We started talking about human insulin. I told this story to the writer who wrote the book—

Hughes: Stephen Hall.[1]

Crea: Yes, as I remember in that book, Swanson, very pleased with the progress that we had made in the laboratory, looked at me and said, "Roberto, how long will it take to make insulin gene?" After some brief moments of silence across the table and after thinking about the size of that first little gene, I said, "Bob, with the chemistry that we are using right now, it shouldn't take more than six months." I remember that answer didn't create a lot of enthusiasm on Itakura's face who said, "It's going to take a lot more than that."

Bob looked at me and said, "If you think that you can do it, you should go ahead and do it." That was probably the go-ahead for the group at City of Hope to start designing the human insulin gene from scratch! Itakura and I spent several days to develop a strategy to assemble the two genes that code for the two insulin protein chains, A and B, out of twenty-five oligonucleotides. necessary for the systematic assembly of independent genes for B-chain and A-chain. So, from that evening at the restaurant with Swanson, Keiichi

1.Stephen Hall, *Invisible Frontiers: The Race to Synthesize a Human Gene*, Redmond, WA: Tempus Books, 1988.

and I started drawing up a plan how to subdivide the genes into DNA fragments which would overlap for stability and be ideal chains, both for the synthesis and for the enzymatic ligation. Ligation is an enzymatic way to fuse together oligonucleotides that line up as a double-strand DNA and have gaps between units. So, in the lab we did some planning on paper, to design first the fragments and the genes and finally we got down to a sequence consensus and a strategic chain assembly plan, which was approved by Keiichi Itakura and Swanson. In essence, we had to synthesize a bunch of oligonucleotides, spanning from eight bases long to fifteen bases long—maybe there was only one seventeen bases long—from our library of dimers and trimers.

In order for us to maximize the effort and minimize the time to complete the project, we took the twenty-five oligonucleotides, and we started breaking them down into blocks. The idea behind that was, to use dimers and trimers, which we could make very well now in large quantity with the new chemistry, and try to use the same blocks over and over for the project. If you do design a trimer block, you have sixty-four possibilites out of four natural nucleotides and the genetic code. In theory, you have to synthesize all sixty-four to cover all of the possibilities. But if you avoid making all of them, that translates in saving time and money. In our plan, we divided the twenty-five fragments in such a way that you can reuse the same dimer or trimer several times, just because you've designed a synthetic strategy that maximizes the occurrence of the same block. Then you don't have to synthesize sixty-four. We succeeded in that strategy because in the end we had to synthesize twenty, maybe twenty-five blocks, between dimers and trimers. That was really a big asset that we had built and stored in the refrigerator, which we then used for manufacturing the insulin oligonucleotides and many other projects.

Hughes: That strategy was worked out when Swanson came down to City of Hope?

Crea: No, that strategy was out of Swanson's direct influence. It was chemistry. Swanson never really was involved in such details. He was relying on the fact that we knew what we were doing.

Hughes: So this strategy was something that you and Itakura worked out?

Crea: Yes, Itakura and I worked out the scheme. I was responsible for managing and executing the plan. In essence, I was the head chemist in the lab who would create these pieces and put them together, block by block, until we had all the molecules purified and ready to go.

Hughes: Was this arduous work?

Crea: A couple of things. First of all, it wasn't easy to purify the dimers and trimers in large (several grams) scale, for a simple reason: to make grams of your final product, you have to start with a larger amount of building monomer blocks. We were starting from three, four, five grams of each individual component and then out of the synthesis and purification, we would generate a couple of grams of dimer and trimer, which in turn were the building blocks for further oligonucleotide synthesis.

The problem was that we had to do everything manually. I remember I developed a fast purification of these building blocks, which helped quite a bit, which was based on silica gel chromatography, on a sintered glass funnel under suction by a water pump. This method was called, jokingly, a "two-fingers" purification because the amount of silica gel

that we would put on the funnel was about two fingers in height. It was sufficient to remove from the end product the monomer components which didn't react. It worked very well. That concept was eventually picked up by a manufacturer who developed a piece of equipment, an HPLC, with silica gel cartridges for the industrial scale purification of DNA and other molecules. Later on, we purchased one of those pieces of equipment, which allowed us to do the block purification automatically, by a machine, but initially it was done by hand. We were using a lot of solvents to the point that we were taking everything directly from five-gallon cans and pouring it into vessels. It was a big volume, a big operation. It was time-consuming and tedious because we had to do it so many times.

At that time, another DNA chemist joined the City of Hope team from Poland. His name was Adam Kraszewski. Adam was a skilled chemist. He had experience in DNA chemistry from his laboratory in Poland, headed by Professor Wieverosky. So there were three Ph.D.'s involved in synthesizing the blocks and the fragments for the human insulin genes. Ultimately, the work was shared equally between the three of us. Adam became my roommate in Pasadena. We shared an apartment. There were days when we would go back home, both of us smelling of all the pyridine and other solvents that we had used during the day, and it was awful because even a hot shower wouldn't take off the awful smell of the pyridine from your skin.

Hughes: What about your health?

Crea: At that time, we were all expert in chemical laboratory and not paying particular attention to our health—it wasn't that we were not aware of the potential toxicity of some chemicals—I think it was in part because we were working under safe conditions in a lab with good fume hoods, so most of the solvents were sucked up by the hoods. But in effect, there was so much excitement in the lab that even occasional episodes of solvent spills did not bother us. We were cranking, literally, molecule after molecule, in a frenetic race to get there first and fast. We didn't spare anything. We put our heads down, and we created a beautiful episode of efficiency and productivity. I remember that not only we finished the synthesis ahead of time, but that we got the great news that the A-gene for human insulin had been assembled very easily. This first part of the project went indeed very, very smoothly. The B-gene, which was a longer gene, was also assembled from DNA fragments. But we had a problem with just one fragment, and that problem ultimately slowed down the molecular biologists in San Francisco. But we didn't know whether it was the fragment or whether it was the gene assembly. In the end, we resynthesized the fragment and repurifying it. It really was a well-oiled machinery that we had put in place for a very important scientific challenge to get first to the completion of synthetic genes for human insulin. That was really all that was in our mind. The rest of the time, and away from the lab, Adam and I used to play tennis on the courts of the Caltech, in Pasadena, whenever the L.A. smog wasn't so heavy to mess up our throats and lungs. We were keeping ourselves good company.

Hughes: So, he became a friend?

Crea: Yes, we became friends. We shared our European heritage and the love for jazz music besides battling on the tennis court. The first time I took Adam to a supermarket in Duarte, in Pasadena—it was one of the first days after he had arrived in the United States—he was totally shocked. Poland at that time was still under the communist

regime, and he was mesmerized by the amount of food that he saw in one place, bottles and cans and boxes. It was really a cultural shock for him.

Hughes: How had he gotten there?

Crea: Adam was a postdoc fellow who had been recruited by Itakura and Swanson, in a similar fashion as I was, from a laboratory in Poland, also known for working with the phosphotriester chemistry. Adam arrived in California three, four months after I did.

Hughes: Was he being paid by Genentech as well?

Crea: Yes. We were both hired as postdocs in the biology department at City of Hope, and we earned a decent salary. Adam had left his wife and one kid in Poznan and was planning to return to Poland after one year in California. He wanted to save money for buying a house in Poland at his return.

Hughes: Did you have an opinion about the chances of success for expressing a mammalian or a human protein in a bacterium?

Crea: After the somatostatin's successful expression, we were confident that we could produce A-chain and B-chain individually by the same fusion strategy. There was no reason to doubt that the same approach used for the expression of somatostatin would eventually work for A-chain and B-chain. However, the problem with insulin was compounded by the fact that the two chains, both bigger than somatostatin, had to be put together to form one molecule through two disulfide bridges. We didn't know whether the reconstitution in vitro would work. There were experiments published in the literature showing that you can take insulin, break down the molecule into A-and B-chain and then recombine them again to form an active molecule, but nobody in our team had any direct experience with protein chemistry. We had a plan to produce enough fusion protein in the bacteria that eventually we could isolate the A-chain and the B-chain in milligram quantities and then do some experiments in vitro to recombine the two chains.

At the same time we were working on the assembly of the genes for A-chain and B-chain, I remember that we had a back-up strategy just in case we were not going to be successful with that first strategy. The alternative experiment indeed involved the use of a third gene for the C-chain as in nature. While the A-chain and B-chain were assembled, cloned, and expressed by our molecular biologist colleagues, we at City of Hope were working in the laboratory to create a gene for a mini C-chain. Mini C-chain means that we didn't want to copy exactly what nature uses, i.e. a C-peptidic chain to fold the A and B into an active insulin molecule. Because the C-chain was a long peptide, at least as long as the B-chain, it would have been another major challenge to build a gene for the C-chain in a short time. So we started thinking of an expedient to reduce the size of the C-chain to the bare minimum based upon scientific data that by this expedient the two chains, A and B, could be lined up by the presence of the mini C-chain in between them, and then folded in a correct fashion. In effect, what we were toying with at City of Hope was the first experiments of protein engineering. We were trying to come up with a modified protein which didn't exist in nature. The presence of a mini C-chain could keep the two chains aligned so that they could form the disulfide bridge. Then, obviously, the strategy involved a process to remove that mini C-chain to create the native molecule.

Hughes: That's indeed what happened?

Crea: Well, we postponed using that strategy because eventually the A- and B-chains were expressed separately, and ultimately we succeeded in reconstituting the human insulin by the first strategy. That mini-C experiment was picked up later on at Genentech, in 1979.

Hughes: Stepping back even further than that, you didn't see any fundamental problems with expressing a human protein in a bacteria?

Crea: At that point, it was clear that the bacteria would not make any dramatic distinction between a human synthetic gene and a bacterial gene. Let me explain better. When we designed a gene for human insulin, we selected the codons for the insulin amino acids to be compatible with bacteria genetic preference. In other words, we didn't try to create a human gene. We created a synthetic gene with codons which would be very close to the ones that bacteria would use, but that would ultimately give us the human amino acid sequence. We tricked the bacteria in that we picked the codons artificially to be an easy ride through by the bacterial enzymatic repertoire and to maximize the efficiency of gene transcription and translation (expression).

Hughes: But not very much was expressed.

Crea: Well, the A-chain was expressed—

Hughes: Oh, I was thinking of somatostatin.

Crea: When we did the insulin experiment, the A-chain was expressed nicely. I remember that particularly, because ultimately everything came back to me. After expressing the fusion protein in the periplasm of *E.coli*, the broth containing the cocktail of proteins isolated from our bacteria was ultimately given to me for HPLC purification of the A-chain. The same HPLC which I used for the cleanup of the oligonucleotides was eventually used with a different solvent system to purify the A-chain and B-chain. So I knew that A-chain wasn't a problem. When they gave me the crude and I ran it through the HPLC, I saw a nice peak corresponding to native A-chain which we isolated, and we set it apart. The A-chain was okay!

The problem came with the B-chain, mainly at the expression level, because one of the fragments of the B gene was not ligating well, so we never got the B gene in good shape. So, once again, back to the bench for the resynthesis of the infamous oligonucleotide. But once we did provide the new fragment—the B-chain was expressed as fusion protein as well. Although the B-chain itself was a little bit more difficult to purify by HPLC, ultimately the two chains were purified and collected in sufficient amount and given back to the group of Professor Riggs for the in vitro assembly.

Hughes: I was wondering what Riggs's part was.

Crea: Riggs's laboratory was part of the Biology department of City of Hope and played a substantial role in the Genentech–City of Hope agreement. The lab included several people with background in biology and molecular biology, but they were doing a lot of biochemistry as well. Riggs provided directions. His laboratory was involved in the processing of the fusion protein, purification and characterization of the recombinant

somatostatin, and of course they also played a very important role in the assembly and characterization of human insulin. In particular, there were, I believe, one or two people in Riggs's laboratory dedicated to support the Genentech experiments.

Hughes: How much were you seeing Dr. Riggs? Was he in and out of the lab?

Crea: Although physically the Biology labs were two or three hundred yards away from our chemistry lab, we were seeing Dr. Riggs often. During the lunchtime, we used to get together in the cafeteria to talk about the progress of our experiments. Often we were getting together for social events. I remember a party at his house and others at Keiichi's house. Even Professor Susumo Ono, the head of the Biology department, gave a couple of parties. So we were all getting together quite often to share lab experience, as well as to socialize outside the working environment.

Hughes: Had the decision been made before you came to use the lac promotor and the beta-gal gene?

Crea: Yes.

Hughes: Who made that decision?

Crea: I think that was a contribution from Boyer's group. Boyer, together with Paco Bolivar and Herb Heyneker, were mainly responsible for the design of the plasmids. What happened as we started using the plasmid system of expression, Dr. Riggs started looking at the possibility of using restriction enzyme sites, which are often unique breaking point[s] along the DNA of a gene, to insert the synthetic gene. I remember in the case of the plasmid that we used, pBR322, it included the lac promotor preceding the beta-galactosidase gene. In the coding portion of the beta-gal gene, there were two Eco R1 sites which could be used for inserting our synthetic genes.

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Crea: Dr. Riggs was looking at the best possible strategy for the cloning and expression of the synthetic genes and the presence of specific insertion points in the bacterial DNA turned out to be perfect for our strategy. The reason why the lac operon was selected was also because it had a convenient promotor for induction of expression, and an EcoR1 restriction enzyme site just immediately after the ribosome binding site, which was very convenient for cloning the synthetic A- and B-genes.

Hughes: Was that common knowledge?

Crea: Yes, you could get that from the published literature. The beta-gal gene however had one more feature that turned out to be very useful for small proteins; it was a second restriction enzyme site at the end of the beta-gal gene, which eventually turned out to be a better site for the somatostatin, the A-chain and B-chain, in that the resulting large fusion protein, mainly beta-galactosidase with the end of the protein fused to the target mammalian protein, avoided the protolytic degradation of the small proteins by *E.coli.*

Hughes: Genentech contracted with UCSF, Caltech, and City of Hope for somatostatin. What did Caltech contribute?

Crea: Well, I can tell you a nice story about Dr. Richard Scheller [laughs], who is currently the vice president of Genentech for research. When I arrived at City of Hope, Dr. Scheller—actually at that time he was a student, working for his Ph.D. thesis—was working in Dr. Itakura's laboratory. He was trying to synthesize a palindromic oligonucleotide which in reality anneals to itself as[a double-strand chain and which contained the DNA sequence for a restriction enzyme, EcoR1. The reason for that work was to provide a sufficient amount of DNA to obtain some crystallographic data of the enzyme and the substrate itself to figure out how and why the EcoR1 enzyme interacts with this fragment of DNA, which as many other restriction enzymes sites, includes DNA palindromic regions. A palindrome is a symmetric sequence which is recognized by various proteins as a unique binding and cleavage site. So, that was the work that Mr. Richard Scheller was doing at the time that I got there. Richard was working at Caltech in Dr. Richardson's lab, and I think that structure of proteins was their main work , but it was of no consequence for the experiments that we did on somatostatin and insulin. It was part of the research conducted at Caltech.

Mr. Scheller managed to get some shares of Genentech early on from Bob Swanson because of this research at Caltech. The day the South San Francisco company went public, there was an article in *Newsweek* magazine, showing the picture of Richard Scheller happily looking at the fortune he had made by being one of the first stockholders of Genentech. The title of that article was "Instant Biotech Millionaire." I imagine neither Richard Scheller nor Bob Swanson had thought that five hundred shares, which was the number of shares Mr. Scheller had received from Genentech, had become so valuable as to represent a lot of money.

Hughes: Had you been offered Genentech shares while you were at City of Hope?

Crea: No, when I was at City of Hope, I was not offered shares. I did not even know that such a thing existed until after I accepted a job with Genentech, and even at that point I was totally naïve, as an effect of coming from a different world. I didn't realize the importance of shares until late; I accepted the job offer as it was offered to me by Bob Swanson with a great deal of enthusiasm and no negotiation. I was already satisfied with having a decent salary, but more than anything else I was very thrilled to have a chance to staff and direct my own laboratory. The job offer I got from Swanson did not contemplate the small number of shares which was given to me after I moved to San Francisco and started the DNA laboratory.

Hughes: But they were not really an incentive? You would have gone without the shares?

Crea: Yes, I would have gone without shares. I remember one episode when we had a dinner with Tom Perkins, in Long Beach. This time we were celebrating the big success of human insulin. I was sitting next to Tom Perkins at the table and during dinner I asked him a simple question, "Tom, what do you do with the shares of Genentech?" "Well, my suggestion is that you put them in a drawer and you forget about them. One of these days, you'll find out that they are worth a lot of money." That was very good advice. In retrospect, I could have negotiated a better deal with Swanson before I joined Genentech. I have to be very grateful to Dennis Kleid and David Goeddel, who were hired to join Genentech in South San Francisco, for renegotiating with Swanson on the shares. At the time I was moving from City of Hope to South San Francisco, they negotiated a deal

better than mine. As a result of that agreement, Swanson decided to adjust the number of shares to be more compatible with those of Dr. Goeddel and Dr. Kleid.

Hughes: Was there ever any questioning of why you would go from what up till then had been a strictly academic career into industry?

Crea: In my case there was no issue whatsoever because I never felt that the Genentech environment was different from an academic environment. I must correct myself: Yes, there was more pressure. Yes, there was more focus, but in the end we were driving a brand new technology and we were performing brand new work, and generating discoveries almost every month. So the environment both at City of Hope and at Genentech was in some extent similar to academia but more exciting in that we could finally foresee the benefits of what we were doing in the lab. For me personally, I never felt any pressure in going from Leiden, an academic laboratory, to City of Hope, a medical institution, and then from City of Hope to Genentech in South San Francisco. I enjoyed quite a bit of freedom and control at Genentech while developing new things, and that was very important to me. I didn't mind at all the challenge of exploring uncharted territories for a private company, such as the one of producing out of microorganisms useful proteins for medical and business applications. I thought that ours was first a fantastic scientific challenge; the business implications at that time didn't have any influence on my scientific decisions. Beside the fact that I wasn't involved in the business aspects and they were too far in the future to bother about. For me, it was more building an exciting career in research, a dream come true and I was getting that opportunity, both at City of Hope and Genentech.

With the success of the company, it became clear that some people started focusing on this unusual migration of brains from academia to private industry and they did not like it. They made a big deal out of it, to the point that you could read titles of articles such as: "Prostitution of brains in professionals by accepting offers by private industry," "mercenaries of science," et cetera. Big words, which to me were inappropriate because in the end it was high-quality research, very much oriented research, and I was perfectly comfortable with that notion.

Hughes: Did you notice any shift at City of Hope, compared to Leiden? How was City of Hope, in terms of undirected, basic research? Was it supported? Did it thrive there?

Crea: Well, the profound difference between California and Holland was the strong feeling of a pioneering work. In Holland, we were structured to do certain things, to publish papers, to address scientific chemistry problems. The goal in Holland was to produce a very nice paper, go to symposia or congresses, and let people know who you were and what kind of work you were doing. It was an academic environment. The prestige was having your name on a nice paper, which would be appreciated by peers at University. In California it was more, "Let's go for the big enchilada." [laughter] "Let's build out of the science and explore some exciting commercial opportunities." The idea of building a company, or an industry, was at its very beginning . It was clear from what the press was writing about Genentech that the potential, intrinsic to the technology of recombinant DNA and biotechnology, was huge. We scientists were kind of naïve, young and skeptical in a way, but we were there; we were at the front of the technology, and we were driving that technology. The focus was more on getting there first and understanding the potentiality of our technology and letting Bob Swanson and company's board do the rest.

Hughes: Let's go back to the City of Hope and discuss the recombinant DNA controversy which, when you stepped off the plane at LAX in 1977, was still going on. Had you heard anything about this controversy before you came to this country?

Crea: Yes, the Asilomar meeting was pretty much picked up by the scientific press. It wasn't just a local event; it was something that you could read about in *Nature* or *Science*. So the big controversy over recombinant DNA was pretty much live and kicking when I got to California, but it was something which, honestly, didn't affect my job. I was not directly involved in dealing with these issues. It wasn't my expertise or my field of research. It was only an indirect issue or problem that somebody was addressing and that eventually we would have to cope with, but not to the extent that it would affect my part of the work. The fact that we were doing chemistry obviously insulated our group from any concern about microorganisms. But we were not making jokes about complying in our laboratory with the FDA or NIH rules for recombinant DNA research in that we didn't have to do anything other than make sure that there was a good laboratory practice. The debate was perceived by me and I guess by the other components of Itakura's team as an issue that was discussed among the molecular biologists, an issue which eventually found a happy ending with the publication of NIH rules. Once we knew the rules, we were going to play that game.

Hughes: You mentioned Thomas Perkins, who of course was on the board of directors and also played a prominent role in the early fundraising and direction of the company. How much was he participating? How often did you see him?

Crea: Tom Perkins was an active board member of Genentech and he was very often visiting with Swanson in South San Francisco.

Hughes: I should have clarified. I'm meaning first at City of Hope when you were still working on the—

Crea: At City of Hope, as I said, we saw him after the successful experiment of human insulin.

Hughes: Was that the first time you had seen him?

Crea: That was my first time. He was the only director outside of Boyer and Swanson, who came down to City of Hope to share his excitement and gratitude with the scientists. In my mind he was the mentor, the experienced business guy who would provide Bob Swanson with sound advice and guidance in building a business organization. I remember he was also at the open house when we built the laboratory in San Francisco. He was there together with Mr. Eugene Kleiner, the two VC [venture capital] principals [of Kleiner Perkins], and from time to time we would see Tom in South San Francisco, his red Ferrari Testarossa parked outside Genentech. That was the sign that Tom Perkins was visiting. I remember that he was driving a beautiful Ferrari Testarossa to the labs—wow, that was my dream! We saw that car maybe once a month.

Hughes: What were your impressions of him as a personality?

Crea: Well, Tom Perkins has such a magnetic personality. He's tall, nice looking, elegant. His presence is something that you notice in the room, but also his intelligence and his soft speaking. It was a sign of maturity and knowledge. There was a lot of respect for him at

Genentech. He was considered by everybody as the most knowledgeable venture capital investor in the Bay Area. He came also with quite a bit of successful background, because his name was associated with some of the big successful stories of the Silicon Valley. Of course the fame preceded him and followed him; we knew he had a beautiful house, a beautiful wife, a beautiful life. Tom Perkins was like a living legend—if I am successful, that's what I want to be.

Before we move on from city of Hope to Genentech, I want to say that I met Shirlee Fox at City of Hope, a few months after my arrival. Shirlee was employed in the office of the administration reporting to the director, Eli King. She was involved in the management and monitoring of the budget assigned to Itakura's group. We were spending the money granted by Genentech to City of Hope for the recombinant DNA programs, so one day I walked into the office of Mr. King with Dr. Itakura and I met Shirlee.

What struck me most out of that first encounter was a mix of beauty and positive energy coming out of Shirlee's genuine and natural personal interaction with people; I felt immediately attracted by that spontaneous energy mixed to her exotic natural beauty. Shirlee was my first black American relationship in California, and it turned out to be the most important one in my life. In the following months, we had many opportunities at City of Hope to get to know each other, especially during the lunch breaks, and I believe that contributed to a great extent to bring us closer. As we learned more about our families, our past experiences, and common interests in life, we felt closer. It is still surprising to us how two people apparently so far apart physically and culturally for their entire lives can find themselves so similar and close to each other when it comes to family, feelings for their loved ones, and pride of their culture and experiences. I guess that learning about ourselves and sharing our past experiences contributed greatly to overcome Shirlee's first impression of me, which later I was told included "being short and speaking broken English."

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[Interview 3: August 1, 2002] ##

Hughes: What did you find when you arrived at Genentech and what were your impressions of the company?

Crea: My first formal relationship with Genentech came in the form of an offer letter by Robert Swanson, and the letter was sent to me sometime in the spring of 1978. Bob, as president of Genentech, was offering me a job as the director of nucleic acid DNA chemistry. In effect, he was designating me as leader of the chemistry group in South San Francisco. I was very pleased, of course, to join formally the company and move to San Francisco. We were wrapping things up at the City of Hope. We were still working on a number of projects at that time, even if we had completed the human insulin project, so I decided together with Bob and Keiichi Itakura to postpone my departure from City of Hope to the fall of 1978. In essence, I spent the late spring and summer in this transition mode. I was preparing myself to take the lead and head the effort in San Francisco, but at the same time I was working at City of Hope to complete other projects that we were pursuing in collaboration.

My first day at Genentech started in mid-September of 1978. I remember that because I flew from Burbank Airport to look for an apartment in San Francisco. In the meantime, I was offered by Bob Swanson an accommodation in his apartment in Pacific Heights, San Francisco. So I spent a couple of days, a weekend, looking around to see if I could find an apartment for myself. Ultimately, Bob was very nice to offer for rent a room in his apartment, which had been occupied by Brook Byers. Our understanding was that I would move soon and take over Brook Byers's room and move my household furniture, which wasn't much, to Bob's apartment in San Francisco.

When I arrived, Genentech was still organizing itself. In the summer of 1978, together with Dennis Kleid and David Goeddel, we were in effect designing the laboratories, providing some sketches—how to organize the space in South San Francisco to accommodate different laboratories. I remember that when I first joined Genentech, there was construction going on at the facilities, and my laboratory was being put together with a few rooms and benches. Interestingly enough, the chemistry laboratory was the largest laboratory at Genentech. So, it was very exciting, because we literally started from scratch. We designed the different chemistry bays—the hoods, the benches—from zero.

Hughes: Was this the first building that at the very start was occupied by other companies as well as Genentech?

Crea: Yes, this was the very first building, but I don't remember which companies occupied that building. Genentech had the corner of a long stretch of warehouses, and I remember we had approximately 10,000 square feet.

Hughes: So the construction that you're talking about was internal.

Crea: I'm talking about remodeling an empty warehouse to accommodate laboratories, offices, conference room. That work was completed sometime in October or November

of 1978. I still have pictures of that party when we had the first open house at Genentech, with still a lot of uncompleted furniture. It was an empty laboratory.

I brought from City of Hope one technician, Parkash Jhurani, from Keiichi Itakura's laboratory, and I hired another one, Mark Vasser, from SRI, Stanford Research Institute, so I was putting together the embryo of my team, which was going to be about eight to ten people.

Hughes: So until November or so, you really couldn't do any research?

Crea: No, we were just setting up the chemistry, buying equipment, buying chemicals and doing the very first experiments, so it was at a very early stage. We were not working on any major projects. As a matter of fact, in anticipation of completion of the laboratory and the hiring of people, we were continuing collaboration with City of Hope. Most of the material that had been used for the human growth hormone and the bovine growth hormone came from the City of Hope laboratory.

Hughes: Why was that?

Crea: Because there was an urgency in cloning the bovine growth hormone and the human growth hormone, and the work that the molecular biologists had done led to the isolation of an incomplete gene. In other words, the gene to be used for the expression of human growth hormone required some patching. That was one reason we needed some DNA fragments. But the major reason was that the early experiments with human growth hormone were not successful. One of the hypotheses which had been discussed among the scientific staff was that the very beginning of the gene of human growth hormone had a very rare codon for *E. coli* because it came from a human sequence. It could not have been recognized by *E. coli* and would have been a difficult start for the synthesis of the protein.

Peter Seeburg, who was in charge of that project, discussed this issue in a meeting where Dr. Itakura, myself, Dr. Kleid, Goeddel, and I believe Giuseppe Miozzari were present. We ended up deciding to rebuild the first five amino acids of the human growth hormone by synthetic DNA and to facilitate the transcription of that gene by replacing the human codons with codons which are easily recognized by *E. coli*. That experiment was done by using synthetic oligonucleotides and eventually was a successful experiment.

Hughes: Did you make those oligonucleotides?

Crea: It was still Itakura's lab. We, at Genentech, designed the oligonucleotides, but the ultimate assignment to synthesize them went to Dr. Itakura and his laboratory. At that time, we didn't have the lab ready.

Hughes: Let me clarify. At that point, your role in insulin was over; you'd synthesized whatever DNA was needed. As you well know, there were still people working on insulin, interacting with Eli Lilly, et cetera. But you had dropped off that project?

Crea: Yes, the role of the synthetic DNA group was over after we confirmed that the genes for A- and B-chains were successfully cloned and sequenced. From that point on, it was

more molecular biology territory, the expression in bacteria, and the final purification of the two chains. If you recall, I was also involved in the purification of A-chain and B-chain by HPLC. We succeeded in purifying and recombining the two proteins sometime early in 1978. So from that point on, my role as a DNA chemist and a protein biochemist, involved solely in the purification of the chains was over. I was really more involved in managing this transition from City of Hope to Genentech. While other people were trying to optimize the recombination of A and B, which was essentially a protein biochemistry problem, I was already ahead on additional projects.

Hughes: That purification you did with the HPLC was an essential step, was it not? I understand that one of the reasons or perhaps *the* reason that David Goeddel had been having trouble was because the insulin segments he was working with were not very pure. Am I on the right track?

Crea: Yes. There were two major challenges. One was to get all the oligonucleotides in a pure form so that the assembly of the genes could go easily and smoothly, and then the cloning and the expression could occur. The second set of challenges was purifying the very minute amount of protein which was produced in the bacteria from the hundreds of other proteins that *E. coli* produced so that we could get the A-chain and the B-chain to reconstitute, to combine together, to form the native molecule, the human insulin. In both cases, I was involved because the use of HPLC was under my direct responsibility. Yes, perhaps the episode you are referring to was the gene, which the first time didn't go together very well, and we had to repurify one of those oligonucleotides.

Hughes: When it is not purified sufficiently you get blockage by extraneous molecules that get in the way physically?

Crea: Well, yes, you have a cross-reaction or contamination which makes it almost impossible that two things find each other. It's like a male looking for a female in a haystack. You have to look for the right counterpart. It's a different situation if you have purified and clean molecules. They can find each other very easily. So, that was the case.

As I mentioned last time, the purification of A-chain went very easily, very well, probably because it was produced in high amounts by the bacteria, and also because the separation by HPLC between the A-chain and the *E. coli* proteins was relatively straightforward. But with the B-chain it was a little bit trickier: not only because it was in smaller concentration in the *E.coli* soup, but also it was more difficult to separate it from the other proteins because of its chemical nature, and that is unpredictable. Until you set up the conditions of your purification, you cannot anticipate how the purification is going to be. If you are lucky you get a nice separation right away because you have different entities that separate well under the conditions of the experiment. But if you have, for instance, something that elutes very closely to the target molecule, then you might have contamination. You might have to introduce another step for separating two things that behave almost in the same fashion under the first set of conditions. In experimental work, you start under a certain assumption, and then until you find out from experience, you can't tell how easy or difficult it is going to be. In the end we did purify the B-chain, and we collected enough material—I'm talking about a fraction of a milligram—so that we could run the recombination experiment in vitro, so that we could finally demonstrate that we made a molecule which was exactly the same as human insulin.

Hughes: And it really was? Because you told me last time that you weren't attempting to use all the codons that nature uses. You've told me that in terms of the growth hormones, you were modifying what you needed.

Crea: Exactly. With insulin, nobody had isolated the human gene. That was one of the reasons that we were so much under pressure at City of Hope and at Genentech to finish fast. We were designing the gene from the amino acid sequence—

Hughes: And working backward.

Crea: And working backward. We were looking at the human amino acid sequence, which was known, and working backward to design a possible gene for the protein. But the gene we designed was arbitrary in the sense that we picked codons for each amino acid that were easily recognizable by *E. coli* as its own. So we tricked the bacteria to work hard for us, giving them a blueprint of human insulin which was compatible with the t-RNA repertoire of *E.coli*.

Hughes: Was there enough variation from the natural human insulin gene that you had doubts whether what you had produced would function?

Crea: No, we were confident that the genetic code would apply to the work we had done. In other words, you can pick among different codons, but the codons that we selected were still coding for the human insulin's amino acids. The choice was really among different codons which coded for the same amino acid, but that choice was dictated by what *E. coli* liked rather than what the human cell liked.

Hughes: You knew what *E. coli* liked because of the somatostatin work?

Crea: No, we knew the preference in *E. coli* because of the database that had been generated out of a virus that infects *E. coli*. In other words, there is a virus, lambda virus, that reproduces itself well in *E. coli*. It can use the machinery of *E. coli* to reproduce itself very fast. There was a sequence of the viral genes and there was a table which shows the occurrence of the codons in the DNA of that little virus. So we took that as the basic rules to optimize the transcription and translation of human insulin A and B in *E. coli*. So we borrowed from a very small virus the secret of how *E. coli* protein synthesis machinery works better.

Hughes: Had that data been published?

Crea: Yes, it was published.

Hughes: So you just turned to the literature.

Crea: Yes, we took the database out of the literature, and then one by one we looked at the different possibilities, and we picked the ones which gave us the highest occurrence in the codon choice of the virus. Today, the same criterion is being used for plant proteins which need to be produced in bacteria and a lot of human genes that are cloned in bacteria. So it's almost like redesigning the blueprint to fit the preferences of the microorganism which is used. That worked out pretty well and was an effective piece of work.

Hughes: What did you know or not know at City of Hope about Genentech's relationship with Eli Lilly?

Crea: Well, one of the first corporate partnerships that Bob Swanson targeted once we started the insulin project was Eli Lilly. It was clear to everybody in the company that Eli Lilly was the largest manufacturer and marketer of bovine insulin, and they were recognized as number one in the world for commercializing this drug for diabetics. So, it was the obvious choice for the Genentech CEO and president to approach them and establish negotiation with them. We knew that there was an interest at Eli Lilly to evaluate any other alternative manufacturing technology to produce a human version of their drug. We also knew from medical literature, from experts in diabetes and insulin that the bovine insulin wasn't really an ideal drug for people with diabetes. The bovine insulin after prolonged use caused some problem as related to immunogenic and antigenic response, and that a number of patients were suffering from side effects. The side effects ranged from typical inflammatory processes all the way to blindness and even some cases of more debilitating diseases.

It was clear that there was a huge opportunity for Genentech to establish a partnership with an industrial pharmaceutical company. The diabetic population was increasing dramatically, bovine insulin was produced from animal glands, and it was a very cumbersome manufacturing procedure, also subject to possible contaminations. Finally, due to the rate of occurrence of diabetes, there would have been an increased demand of insulin that the animal organs would not have met. So, there was a huge technological opportunity for Genentech and there was a clear business target, which was Eli Lilly. Swanson started negotiating with Eli Lilly, specifically with Irving Johnson, who was Lilly's lead person, the champion, for exploring alternative manufacturing technology for Eli Lilly. So, we saw people coming from Lilly to Genentech, or we heard of meetings of Genentech management with Eli Lilly. As we were continuing working in the laboratory, we knew that was an important milestone for the company. We also knew that we were not completely off the hook in that after the announcement that we had produced human insulin, I believe that Eli Lilly became more interested, but ultimately they were asking some tough questions to complete the negotiations and cut a deal.

Hughes: I've heard it described that Eli Lilly wanted to see the insulin. Genentech could talk to them forever about the new technology but Lilly wanted—

Crea: "Show me the molecule." [laughs] For us, obviously, it wasn't a trivial exercise to produce a milligram or even grams of the molecule. The major accomplishment at Genentech had been the demonstration in the laboratory that this was a viable technology, but we never did any scale-up production. But, it really was facing reality for the company, in that the recombinant technology was just a component of the whole story. Genentech would have to address additional important questions, such as manufacturing, scaling up, purity, characterization, and down the road compliance with the FDA and a body of regulations typical of the pharmaceutical industry before we could claim that we had made a drug.

Hughes: But Genentech, at that stage, never contemplated doing that whole entire process, did it?

Crea: No, Genentech wasn't at the stage of claiming to the world that the company would become a fully integrated company. We were still promoting the company as a unique, technology-driven organization. It came later, after the success we had with human growth hormone. That decision matured in Bob Swanson's mind. In retrospect, I believe that the exposure and the experience and the relationship with Eli Lilly was very instrumental to educate Swanson and the rest of the team how you become a fully integrated pharmaceutical company.

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Crea: If you took a snapshot of the company, you could see that the momentum was building, because there was a lot of interest by the investors and that the management was making the right decision, namely to bring in extra expertise for downstream process. If you remember, one of the icons that characterized Genentech in the early days was a fermentation apparatus which we built in the warehouse. Although it wasn't used very often, because we didn't have much to do with it, it was a very nice icon. We took a lot of pictures with the investors. That was essentially the challenge to Genentech: to become a manufacturer of important protein-based drugs. Ultimately, the company was capable of adding expertise in fermentation, in protein purification, in protein characterization, and eventually all the way to scale up and purification under the GMP [Good Manufacturing Practices] and so on. It was almost like a pipeline which grew, having in mind this fully integrated organization which didn't want to depend upon anybody else to discover and develop its own drugs.

Hughes: How much were you and the other scientists in the loop as to what Bob Swanson and the other executives were doing?

Crea: Well, we were quite involved. I remember that we used to have staff meetings almost every week. Those staff meetings would involve all the major players, from scientists to attorneys to Bob Swanson, of course. We started discussing the business aspects in addition to the scientific milestones. Also, because a lot of the early scientists were becoming involved in negotiation of major deals. I remember the role that Dennis Kleid had early on in negotiating a deal with Plum Island and the Army for developing a vaccine for foot and mouth disease. I remember myself, being involved pitching to Hoffmann-La Roche the human interferon project. I remember traveling together with Swanson and Herb Boyer to New Jersey and having a meeting with the Roche management to talk specifically about a corporate relationship for the development of human alpha interferon.

Hughes: And they wanted you to come, because you could speak to the science?

Crea: Correct. Sometimes I would go and other times other people would go. So, the science and the business became mutually supporting. We provided the technical contribution. But as we met more and more managers from the pharmaceutical industry, we started learning the language, we started learning the rules, we started learning the dynamics that supported the relationship. That was a really unique school for many of us, and if today a lot of scientists have become managers, especially out of Genentech, it is because of that exercise that we went through over and over.

The scientific presence was extremely important for selling things, because everybody was looking at Genentech as the pioneer, the best in this new industry called biotechnology. They wanted to hear directly from the scientists about the novelty, the uniqueness of the products and of the science. So we were very much involved. Not everything of course was told to the scientists, and I remember sometimes there was some uneasiness, if not a manifest complaint, with Bob Swanson of keeping us scientists in the dark. The makeup of Genentech in the early days was mainly scientific, with the exception of Swanson and some external expertise provided by Tom Perkins and Tom Kiley. Ninety percent of the players were scientists. We were the majority, and we had power in the organization. We were imposing on Bob to be more communicative, to involve us more often in his business decisions. It was a very dynamic, very interesting environment. We managed to elect a representative of the scientific team to be present in each and every business discussion. Whether that happened or not, I don't remember, but I remember that there were a number of discussions with Bob addressing the specific need for the scientists and the key players to be informed about business decisions.

Hughes: Did scientists appear before the executive board?

Crea: No, the board was more an abstract entity for the scientists. We knew about it, but we never had a direct participation. Early on, the board was formed by only a few people—Herb Boyer, Bob Swanson, and Tom Perkins. We learned that as more and more companies were investing in Genentech they would have a presence at the board level. For instance, Lubrizol, which was one of the early investors in Genentech, asked for a board seat. Don Murfin represented Lubrizol for many years. Later on, the board grew to include experts in the field. This kind of event happened once more when Alpha Laval made an investment in the company, and a representative of Alpha Laval, I guess the president of the U.S. operation, became also a board member. But scientists were not directly involved.

Hughes: Biogen had a really high-powered scientific board with several Nobel Prize winners. But Genentech didn't go that way. Was it ever a discussion point, "Why don't we have a scientific board?" The people on the Genentech board of directors were not scientists, with the exception of Boyer.

Crea: I believe it was self-confidence, almost I would say arrogance—being cocky. We scientists were running the show. We were developing new technologies. We had an unlimited power to come up with new things. Things were happening so fast that I believe it was a mix of not recognizing anyone with the experience to drive that effort and at the same time having Herb Boyer as the founding scientist, as the lead, the scientific visionary as a representative at the board level.

Later on, Bob became sensitive to the need for the presence of key scientists as advisors to the company. I think, in that respect, he relied on his connection with MIT to bring in some heavy-duty, high-powered scientists to advise the company. So it wasn't formally a board; it was more individuals who were hired to provide their expertise to the various departments. In reality, we had access to very high-caliber scientists all over the United States. Perhaps we were more informal, but the spirit of the team at Genentech was informal—too informal, in the sense that we were creating our own story every day.

We had this sense of power in the team that was sufficient to motivate everybody to do the right things.

Hughes: I wonder too if there was an element of wanting to maintain control. If a company has a high-powered scientific board, there could be difficulties. If you want to keep the reins of power within the company, in the hands of Swanson, you don't want a Nobel Prize winner on your board, saying, "Oh, no, that's not how to do things." Maybe I'm searching too hard. Maybe it was just the way the board evolved, the way it happened.

Crea: Well, it's never one or the other. Probably all of these things are true. It's a lot easier for a young manager to have people who are not going to interfere with his job, and that was true for us as scientists. We were not interested in listening to somebody else, because there was too much excitement in what we were doing.

I remember the performance review I had with Bob Swanson for 1979 was very positive. But his final remarks were as follows: "Roberto should seek the advice of highly respected scientists in the field." To be honest, I wasn't interested in it because I didn't want anybody to tell me what to do. I was one of the few chemists in the world who would make DNA as fast as we did, and I didn't want any interference. I didn't want to have to explain to somebody or to have the consensus of somebody. In retrospect, I didn't react very well. It could have been different. I don't know whether it would have made any difference. But I remember specifically that I didn't want anybody to provide alternative ideas because I was perceiving that as a possible interference of my work. I didn't want to talk to any gene machine expert. I didn't want to talk to any DNA chemists, other than my colleagues. There was pressure by Bob, because he had a chemistry background, to bring in some of his professors from MIT. Ultimately, it was give and take: We hired a few consultants from Boston, MIT, and we managed to establish a healthy relationship with individual scientists, rather than forming a scientific advisory board as a body, who would coordinate rather than dictate the scientific operations.

Hughes: Why did Bob suggesting that you should bring in outside expertise?

Crea: I think he was motivated by a number of reasons. The first one was the vision he had in building the very best scientific team in the world. That philosophy was explicitly manifested by Bob on several occasions. His philosophy was, "Let's hire the best." He always insisted on hiring high-quality people. He made a bet on the very best in the field, and he was right. So, he wanted us to do the same, not to compromise with low quality, but to find and hire the very best in the field. The second motivation, I believe, was the fact that we were building a business, and we needed to be recognized by the outside world as the very best. Maybe Roberto Crea wasn't a name familiar to many people and many investors. But if he had had Professor So-and-so from Harvard or MIT, it would have made the overall vision of the technology and the technical team more credible. That is a strategy. That makes sense. I'm not saying that it was motivated by a window-dressing philosophy, but he knew that bringing in the most recognized names would benefit the company from more than one angle.

Hughes: Do you remember ever having a discussion with him on this point?

Crea: Yes, I remember my resistance and my skepticism about involving other chemists with big names because I was afraid they would shed me.

Hughes: But you were very young, despite your accomplishments.

Crea: I was very young. I was still in the mode of establishing myself. More than anything else, I was afraid that a more established name in the industry would take advantage of what we had done to get the credit. I had seen that before, including past experience where you do most of the work, and somebody who can speak well and present well gets the credit.

Hughes: Did you have a relationship with Swanson in which you could say this kind of thing? Could you talk to him in this manner?

Crea: Yes, I had a nice relationship with Bob. I mentioned that we shared the apartment downtown for more than a year, so we were not only involved in the same company as boss and scientist, but we were sharing some relaxed moments in the evening. I was playing in the kitchen. I was experimenting my Italian cooking ability with Bob, and we had many occasions when we could talk freely and share our thoughts with each other. Although during the working hours, Bob was very professional. Outside that he would really come down and be almost playful and boyish with the rest of the team. He was a wonderful person who could put himself at different levels and open up with his colleagues. So, specifically the answer is yes, I told Bob. But Bob was persistent. As I said, I was listening to him as a big brother. I tried not to go one hundred percent his way, but to go his way ultimately.

Hughes: In these first years, the scientists became concerned that some of the new people being brought in did not meet the highest standards. Does this ring a bell?

Crea: It was easy in the very beginning when the Genentech team was still thirty, forty, fifty people to share opinion and decide by consensus. So the hiring we were doing was very good, high quality, because we were all participating. When the company started growing, adding lots of people every week, it became more difficult to monitor that selection or to participate in that selection. So you can imagine that in a fast-growing organization, your colleagues are not interested as much in participating or interfering with your business, and therefore you can enjoy more freedom in your selection. On the other hand, there is more risk because you might hire somebody who ultimately turns out to be mediocre and find out later that you overlooked or underestimated a defect. So, in a way it is a positive and negative having total control of the decision in bringing in new people, because one person's judgement is not as good as that of many people. It's possible that later on, some of the people hired at Genentech didn't turn out to be as good as we thought.

Hughes: It may have happened after you left, but somebody talked to me about a hiring committee because this problem of mediocrity had gotten to a level where people thought something had to be done—that it wasn't acceptable to have a division head on his own hiring a new scientist without some common set of criteria. I thought that it was formalized as a committee, but I may be wrong; it may have been more informal.

Crea: No, I don't remember. Maybe it happened after I left. My experience in the company was a mixture of success and failure. I hired early on a chemist who turned out to be an arrogant person who gave us a lot of headaches. At the same time, we hired another person from Yale University who turned out to be a wonderful scientist and a wonderful person. It's really difficult, hiring and selecting people, even if you have a committee. But it's true having more than one person, especially people who are trained to see through the façade and the good things that you hear from candidates, ultimately minimizes the risk of hiring mediocre people.

Hughes: I should have asked this earlier. Did you go to the press conference announcing human insulin in September, 1978?

Crea: Yes.

Hughes: Can you describe the situation?

Crea: I remember that that was a big event, but it wasn't my first press conference, because, as I mentioned before, I participated in the first announcement by Genentech of the successful experiment with somatostatin. The City of Hope press conference was obviously more important. It was a clear disclosure to the world that this technology that we mastered was going to become an important component for the pharmaceutical industry, and perhaps for many other industries, like the food, the environment, the energy. It was a major show which was planned carefully by both Genentech and City of Hope.

Hughes: Was one of the points of the press conference to show the attendees that this technology could do far more than produce just insulin?

Crea: Swanson had that message in his presentation. But I believe that at that conference, more than the broad applicability to the industry, the focus of the presentation was on health care, the benefit to humanity from a medical standpoint. The strong message was, "Now we can make for the first time a human protein which will benefit millions of people. If today we can make insulin for diabetes, tomorrow we'll be able to make other drugs for people with devastating diseases, like cancer or cardiovascular." So the emphasis was the power of technology for medicine, for saving lives, or for providing a slew of new drugs.

Hughes: Were those goals a motivator for Roberto Crea?

Crea: For me it was like Disneyland. It was a wonderful set of events. I was flying high. I was in the picture, contrary to what had happened for somatostatin where the focus had only been on Dr. Itakura and Art Riggs. The insulin breakthrough officially identified Dr. Roberto Crea as one of the protagonists of new technology—the biotechnology.

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Crea: From that point on I was treated as one of the major players, and I believe I deserved that. It was fascinating how the laboratory events had unfolded in a worldwide front-page media event, and I was enjoying every minute of it.

The City of Hope press conference had two tables, one on the left side of the podium with the City of Hope scientists. I remember it was me, Dr. Itakura, Dr. Riggs, and Tadaaki Hirose. On the other side of the podium was the table with Robert Swanson, David Goeddel, and Dennis Kleid. The chairman of the meeting was Dr. Rachmiel Levine from City of Hope. The conference started with an introduction by Dr. Levine, followed by a presentation by Bob Swanson. The flash of the photographers' bulbs, and the noise of the cameras, and the heat of the day, and the crowd were all a fantastic and surreal experience. I didn't get a chance to get up and talk about my work because in the midst of the presentation we had a power failure. Not that I was one of the main speakers, but I was ready to answer questions if somebody in the press would have asked about the synthesis of the genes. But as Dennis Kleid took the microphone and started talking about the importance of the discovery, we had a power failure. That could not be fixed, so the media started to leave the room, and we took some journalists for a tour of the laboratory.

Hughes: It was a new experience for you.

Crea: Well, I had just accomplished thirty years old in July, so for me it was an incredible adventure. It was so exciting to make history and to see my name published in the newspaper or in scientific magazines. It never happened to me before and it never happened again in that form.

Hughes: Is there a story about the published papers? There are two of them: one by the cloning group and one by the DNA synthesis group.

Crea: Correct. There was pressure on the group collectively to publish the data before we had a press conference. Otherwise it would have been perceived as bypassing scientific integrity, and in that respect, we didn't want to disclose anything to the press prior to a scientific paper being accepted by one of the most prestigious journals. The two papers were prepared to describe the two aspects of the insulin story, namely the chemical synthesis, and the cloning and the expression. Obviously, in terms of news and scientific importance, the production of insulin was bigger news. So the focus was on getting first the expression work ready for publication and later on coming up with the synthesis of a human insulin gene. We managed to get on a fast track, because the policy of the journal that we targeted, the *Proceedings of the National Academy of Sciences*, is that if the paper is reviewed and submitted by a member of the Academy it is automatically accepted. So we managed to get the review of Professor Ernest Beutler in Chicago.

Hughes: Somebody on the team must have known him—right?

Crea: Professor Beutler was a member of the academy for his contribution in biology, I think, but he was also a professor at the City of Hope.

Hughes: Probably Riggs set it up?

Crea: Riggs must have set it up.

Actually, I have to correct myself: the chemistry paper came first. The chemistry was published in December, 1978, and the expression paper came a month later. But they were submitted side by side—October 2 and October 3,1978.

Hughes: Is there a story there? One could argue that it made sense to publish them back to back in the same journal issue.

Crea: It must have been some detail in the paper, some comments by a reviewer, that postponed publication of the expression paper. Yes, it would have made sense to have them side by side. Actually, if I remember well, it's not that. It's a policy of the *Proceedings* to publish not more than one paper every issue by the same author. So, we couldn't publish side by side in the *Proceedings*. So, we compromised with the publication of the chemical synthesis and immediately after came the expression paper.

Hughes: Who are the authors?

Crea: In the chemical synthesis, obviously I didn't have to insist that I would be the first author. In any event, it was okay, because Dr. Itakura was the senior author, and he was the last, but I was the first. This is still if not the most important publication that I've done, one of the most important publications. The other paper had Goeddel as the first author and Dr. Riggs as senior. So, we were happy. I worked on the chemistry paper together with Dr. Itakura, and of course our strange English was probably edited by the rest of the Genentech team. But we got the paper in good shape to provide the most important experimental design and details. It got accepted and published two months after we submitted it.

Hughes: That was very quick.

Crea: It was very quick, but the nature of the work was unique.

Hughes: It was evident in the expression paper that Goeddel should go first and Riggs should go last, but the order's not evident for the people in between, of which there are many. Was there any discussion?

Crea: Yes, of course. There was a discussion among the authors. I believe that the criteria which were used identified the Genentech team, the San Francisco team, as the most important authors of this paper, and City of Hope as second important. So, the names in the insulin expression paper refer to the San Francisco team, namely the Genentech team and the UCSF team. Later on, the order of the authorship reflects the contribution of the chemists, mine and the others, and finally Art Riggs as a senior author as one of the key people in preparing the experiments.

Hughes: The conceptual basis?

Crea: Yes, in the conception of the expression. Interestingly enough, Dr. Boyer is not part of this paper.

Hughes: Exactly. [Pause.] Are you going to explain? [laughter]

Crea: I believe that it must have been a very tough decision. I can't be sure that I understand all of the reasoning behind the decision. On one side, I can say that technically speaking, the work had been accomplished by the authors, and that Herb Boyer was never involved from the experimental standpoint. But obviously the argument that he was one of the minds behind the project would justify the presence of Professor Boyer as an author. So, I believe that it was a mix of scientific rigor as well as perhaps some corporate reasoning to specifically identify the work as generated by Genentech and not by UCSF.

Hughes: That's interesting, because one of the things that I have heard, and I must admit not specifically tied to this paper, is that Boyer from the start of Genentech wanted to step back and give the young scientists a chance. How true was that really? Is that handy to project now?

Crea: No doubt that Herb was the mind behind Genentech science, and if it wasn't for his contribution at the level of recombinant DNA and his involvement with Swanson, there would be no Genentech today. But it was a mix of respect for the young scientists who were making things happen, and I would say also the sense of maintaining a position which could not be identified too much or too often with the industry. Herb was under tremendous pressure as a professor at UCSF not to step too much into the business side of science. He may have decided it was a good thing to do to let the young bright scientists get the credit for taking the technology to the next stage and not to expect to center all the scientific attention upon himself. I think that we appreciated very much at Genentech his integrity. In retrospect, Boyer could have had more visibility as a player at Genentech, but I think that he didn't need it, on one side. He was very sensitive not to be perceived as a person who wanted to take advantage of things in which he hasn't participated, at least from an experimental pointof view.

Hughes: As you are probably thinking, in 1977 and 1978, he was being criticized for having commercial ties while remaining a professor at the University of California at San Francisco. So, maybe it would have only intensified that criticism if he had appeared as an author of a paper on research which in large part had taken place at a company.

Crea: Yes, I believe that there was a lot of criticism and not only in the corridors of UCSF. The press started publishing articles which weren't positive for this hybrid position of a scientist and entrepreneur. That debate went on for several months, maybe years, and it was almost becoming paranoia to get associated with a small business if you had a prestigious position in academia. We were also aware and shared that frustration and that pressure with Herb, because that ambiguity which had been created by colleagues and press continued hunting Herb for many years. We all felt that he deserved to have a Nobel Prize for his discovery and that ultimately his association with Genentech had compromised getting that big reward. Whether that corresponds to reality is always going to be difficult to know. But it was in our mind every day that Boyer was almost singled out by the academic community as this rebel who stepped over the code of scientific integrity and was trying to make himself rich and famous by an association with an industrial enterprise.

Hughes: So there was quite a bit of talk about that at Genentech?

Crea: Yes, we were just sharing his unhappiness and uneasiness, because he never wanted to relinquish his position with UCSF. But he found himself in the eye of the cyclone of biotechnology and the growth of a tremendous industry, which eventually became one of the most exciting revolutions of the past century. Whether he wanted to do that, it wasn't upon himself. It was out of his hands. So, he tried to do the best out of it.

Hughes: Interesting circumstances.

Crea: I can add something else. We as the scientists were very much concerned that the quality of the science at Genentech would be as high or higher than any academic laboratory, because we didn't want to be perceived as mercenaries or second-tier scientists. So in that respect there was tremendous sensitivity and awareness for the quality of what we were going to publish. Fortunately, we had a leader in Bob Swanson with a vision of not compromising quality of the science. So all the publications that came out of Genentech now are considered one of the most beautiful examples of scientific experiments and scientific discoveries.

The discussion of science and the application of science was very much alive among the young scientists who had joined the company early on and the scientists who had joined the company later on because of the impression that commitment to leave academia to join a biotech company was the equivalent of choosing money versus glory. Ultimately that was proven to be wrong.

Hughes: Shall we move to the patent?

Crea: Sure.

Hughes: The Riggs-Itakura patent didn't issue until 1987, but was applied for in 1978.

Crea: Before that. Maybe '76.

Hughes: Were you involved in that discussion?

Crea: No, I wasn't.

Hughes: Why were certain people included and others not?

Crea: Well, in my mind and in everybody's else mind, I believe the conception of producing proteins from recombinant DNA technology was born in Boyer's mind and in Swanson's mind, back as far as 1975 or '76 when they first met. The execution of that strategy essentially took place at City of Hope. The most relevant experiments unfolded as the synthesis of the gene was perfected, as the cloning was perfected, and as we found the expedient to produce a stable protein in *E. coli*. City of Hope was essentially relying upon two laboratories: one was headed by Art Riggs and the other one was headed by Keiichi Itakura. In retrospect, the invention of expressing heterologous proteins in *E. coli* happened in those two laboratories. The patents, which capture the novelty of those inventions, were written to reflect the execution of that plan and bear the names of the heads of the laboratories.

It's a very debatable field. One can make the argument for giving the paternity of those patents to Art Riggs and Dr. Itakura, and somebody can make an equally valid argument to assign the authorship, the inventorship, of those two patents to Boyer and Swanson. The patent law is a very complex discipline and by no means do I want to represent that I'm an expert. But I believe that everybody can understand the conception of an idea and the execution of an idea, so that's where the key issue lies. Should a patent recognize the person who has conceived the idea or should a patent recognize the person who executed the idea, and embellished the idea, and eventually demonstrated the idea? The patent law says that you need two things: to enable somebody who is skilled in the art to reproduce your invention. In that respect, if you don't have any laboratory work, you don't have any invention. I don't believe that the possibility of producing proteins from bacteria, which was conceived by Boyer and Swanson—at least we can assign a portion of that paternity to them—I don't think that that by itself would have been sufficient to qualify for inventorship on a patent. That the only authors should be Professor Riggs and Dr. Itakura can also be perceived as limiting. But these are decisions that are typically discussed among the participants, the players, the attorneys, and ultimately it is what it is. The patents were filed by City of Hope and assigned to Genentech. Sometimes it's a matter of strategy.

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Crea: I can think of a second scenario where the patent could have been filed by UCSF. But UCSF was not involved in the experiments, so they didn't have any title—

Hughes: Well, it was involved in somatostatin.

Crea: They could have filed a prophetic patent. Prophetic means when you conceive an idea that in your mind can be accomplished because all the components that are required for the experimental work are known. But in this case they were not known. We didn't know what to expect from bacteria until we did the experiment. So really the alternatives weren't many. Actually, I should say that there were no alternatives, because the third scenario could have been that Genentech filed for patents. But Genentech at that time didn't have any laboratory or any scientific personnel. So in the end, it was a good compromise from a business standpoint to let City of Hope file under the contract relationship and the understanding that those were patents exclusively licensed to Genentech.

Hughes: Herb Heyneker springs to mind. As you know, he was a postdoc, being paid by Genentech, in Boyer's laboratory at the early stages of the somatostatin work. Then he dipped in briefly in the insulin work when he came back from Holland. It must have been before you arrived when there was a problem with a flipped codon. He and David Goeddel went down to City of Hope and worked furiously to figure out what was wrong—probably not enough to make a patent claim. In the first instance, Heyneker was a UCSF postdoc, paid by Genentech. In the second case, he was only a prospective employee of Genentech. So it is not a really strong case, is it?

Crea: No, it was a complicated situation. In the end, in my opinion, it was a good compromise because there was a clear distinction between the work that was supported by Genentech at City of Hope and the contribution of other scientists at UCSF. It would have been a lot more difficult to share that patent with UCSF and cut a deal with UCSF,

even if you could relate some of the invention to UCSF employees. It was a clear cut. It was reality. It was a good compromise between recognition that maybe not everybody was entitled to participate in that invention and the fact that ultimately Genentech was getting the exclusive rights to exploit that patent.

Hughes: By being the exclusive licensee?

Crea: Exactly.

Hughes: Was that part of the deal?

Crea: That was part of the deal. It was clear that there would not have been any commercial application of recombinant DNA technology without Genentech supporting the effort at City of Hope. So it was clear that any commercial implication of the research that we were doing at City of Hope would have been exploited by Genentech as a company.

Hughes: I meant, was it understood from the start of the patenting process that if a patent issued Genentech would be the exclusive licensee?

Crea: I think that was part of the initial contract. I cannot imagine, although I have not seen the contract itself, but I cannot imagine out of my twenty-plus years' experience in the industry that the company wouldn't expect full rights to a program which is sponsored financially by the company itself.

Hughes: There's a precedent for that, isn't there?

Crea: Oh yes, it's almost the ABC of business, especially when the technological risk involved in the research work is being supported by a company. There was no assurance for Genentech that this would ever work. This situation was contrary to a case when a company goes to an institution—Stanford, MIT, Harvard—and licenses a patent. In this case the research is already done, and the company has the benefit to evaluate the potential, prior to committing any financial means. In the case of Genentech, it was pure speculation that this technology would work. So what would have been the reward for taking the risk other than exploiting commercially the inventions of those patents? Anything to the contrary would be uncivilized.

Hughes: Well, perhaps we could stop with any observations you have about intellectual property policies in those very early days at Genentech.

Crea: It became clear with the Genentech phenomenon that intellectual property was one of the pillars upon which the industry was going to be built. That science perfused from academia into the industry and later on from the industry into the academia is an argument that can be made. It was a cross-fertilization between laboratories at Genentech and laboratories in academia. And it's always the case because science speaks the same language whether it's done by a commercial enterprise or by researchers in academia. But the only way companies can survive is if they have a clear protection from an intellectual property standpoint. So, conceiving a commercial enterprise without strong intellectual property is almost building on sand. So, as the biotechnology industry in its infancy started growing, it became very, very clear that the only way to survive and flourish was to access a strong IP. If you could do it in your

laboratory, it was fine because it was one of the major assets that the company could build. But if you could access intellectual property from academia through licensing, it was also a valuable alternative. So, many companies in the early eighties took the approach of licensing technology from the most prestigious institutions, like Harvard, MIT, Stanford, and Berkeley. That is not different from what happened in other industries, like the electronics industry. But for biotech it was extremely important, almost essential, to rely on intellectual property to build a business upon something unique that nobody else could access. So the patent world got an incredible boost from this new biotechnology. Hundreds of patent attorneys start getting involved in this new field as it became clear that it was an exploratory, fertile ground for inventions for years ahead. Genentech was very smart and very fortunate to have somebody like Tom Kiley early on to take care of that aspect. I think that the work that Tom has been done in identifying intellectual property and protecting intellectual property at Genentech is almost textbook.

Hughes: There were some uncertainties in the early days about patents in biotechnology as a field. Do you remember that patent applications were held up for a while, waiting for the Chakrabarty decision? At the time, there was a fair amount of talk in the press about even if the patenting of life forms is allowed, will these patents stand up? Do you remember any discussion like that?

Crea: I remember very well, because that was a major, major decision for the biotech industry at its early stage. I believe that if the Chakrabarty patent had been denied, it would have killed the industry right there, because most of the work that was being done by biotech companies was centered around living organisms and life and biological events. So that event was saluted with a great deal of enthusiasm by the entire industry. That shows you the visionary, illuminated gift that this country has in supporting innovation and creativity. It's amazing to think of the disastrous effect that it would have had if the Supreme Court decision had gone the other way—the denial of the majority of the biotech patents. So thank God things went the way they went.

Hughes: Was the Supreme Court decision a subject of discussion among the scientists at Genentech?

Crea: Oh yes, although there was a feeling that we couldn't do much about it. We were talking about it. I think that Mr. Kiley played an important role during that period with his testimony before Congress in favor of patenting biological forms.[1] So, if science wasn't directly involved, the representative of intellectual property at Genentech was heavily involved in that debate.

Hughes: Should we stop there for today?

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1.Kiley wrote an *amicus curiae* brief for the Chakrabarty Supreme Court case of 1980 (*Diamond vs. Chakrabarty*, 447 U.S.303 [1980]).

[Interview 4: August 29, 2002] ##

Hughes: Dr. Crea, give me your observations of the atmosphere at Genentech in those very early days.

Crea: We're going back to the beginning of 1979. As I mentioned to you, I got to San Francisco in the summer of 1978, and I was mainly setting up the lab, putting equipment together, hiring some people. The early days at Genentech were characterized by a flurry of activities in that we were trying to move some projects ahead. At the same time, we were recruiting good people from all over the country and maintaining a healthy dialogue with City of Hope. At the same time, we were focusing on some important collaborations with outside scientists, especially scientists who were working on the human growth hormone, insulin, and interferon projects. Specifically, what comes to my mind is a collaboration with Peter Seeburg from UCSF, Axel Ullrich, also from UCSF, and other scientists, mainly from academia. But also we were exploring collaborations with companies, like Eli Lilly and Hoffmann-La Roche. We were also focusing on our own projects, projects which we could initiate internally and carry forward without any additional help or participation by other scientists. It was very intense because the scientists were gathering together quite often in the presence of Bob Swanson, or even without him mainly to discuss the progress of the scientific experiments, but also to look ahead to the new proteins or old proteins that could eventually be produced by recombinant DNA.

Hughes: Was there a lot of interaction? For example, the cloning group might make suggestions to the DNA synthesis group, or vice versa?

Crea: Not really, not with respect to DNA chemistry. DNA chemistry was up and running from the beginning. In essence, the technology had been transferred from the City of Hope. We took with us quite a bit of material, we shared a library of dimers and trimers, but essentially the methodology was well established. We had equipped the laboratory with all the necessary instrumentation to do both the synthesis and purification of DNA. So really there wasn't much discussion around the priorities of my department because since the very beginning my department was perceived as quite productive. So, if people were asking for DNA, they were getting it. It was more a matter of priority: which one comes first? Which one comes later? The basic approach or methodology was never discussed.

Hughes: I didn't mean that so much. But there must have been some coordination that had to be arranged, and you just mentioned that: who needs what primer first? And when might things come from City of Hope? That was still happening, was it not?

Crea: We decided early on that City of Hope would participate in the human growth hormone project. That was dictated by some contingency—the lab wasn't ready at Genentech, so we had to get things going while we were setting up the laboratory, hiring the first scientists. That project was discussed early on with Peter Seeburg, Goeddel, Kleid, Itakura, and myself. Miozzari was also part of that discussion. That decision was essentially unanimous to maintain a relationship with City of Hope and to get the fragments which were necessary to complete the gene from Dr. Itakura's laboratory.

Hughes: You didn't have any adverse feelings about that arrangement?

Crea: No, none whatsoever. I think at that time, I was not too much interested in the business relationship between Genentech and City of Hope. For me, it was something that Swanson had taken care of, and it wasn't our job to dig into the business relationship. Our job was more to get the project moving and done quickly. There was this sense among the scientists that we were in a very competitive arena and in a race to express and produce novel proteins.

Already, with human insulin, there had been a lot of pressure to expedite the synthesis and the expression because we knew that there were other laboratories which were working very aggressively. The word was getting out very quickly that we had a very powerful machinery at Genentech to do more and more, better and better, and address the next challenge. Our assumption was correct in that other laboratories, once they figured out how to do it, once they saw the publications, and they looked at the work Genentech had done with human insulin, were going to reproduce or try to do the things that we were doing. We were trying to put distance between ourselves and the rest of the world by really moving quickly into more ambitious projects.

Hughes: Seeburg of course eventually came to Genentech, but when you first arrived at Genentech, he was still at UCSF. Did you think of him as a collaborator while he was still at UCSF, or was he somewhat of a competitor?

Crea: He was perceived as one of the top leaders in the area of human growth hormone. We knew that he was working in Howard Goodman's laboratory at UCSF. But somehow, from my point of view, we saw Seeburg coming to Genentech early on—it must have been the fall of 1978—with the clear intention of working with us, almost a recognition that he couldn't do it by himself. I knew that we couldn't do it without him. So there was a genuine sense of synergy and complementarity when we first got together in that he was bringing years of experience in the specific cloning of human growth hormone and bovine growth hormone. We were adding two major components to his work, namely the ability to fix the gene which was not complete when he sequenced the gene, and to clone and express the gene in a much more efficient way than he could do it by himself.

Hughes: When you say fix the gene, you are referring to the fact that it was part synthetic?

Crea: Correct, I am referring to the fact that I was told that the gene wasn't complete. The sequence that had been isolated at UCSF was missing a portion, and we had to reconstitute that portion with synthetic DNA. That was exactly what we told Dr. Itakura to do early on: to synthesize the necessary oligonucleotides to build up the portion of the gene which was necessary for the coding region of the first twenty three amino acids.

Hughes: I believe that the San Francisco group was using a complementary approach. Why was the gene incomplete?

Crea: You are correct. The technology at that time wasn't effective and efficient to isolate genes. So the approach they were taking at UCSF and many other laboratories was to start from probes from pieces of the gene and then try to copy the remaining gene. Very often you can pull out only partial sequences, so it is not a given that you can isolate the whole gene.

Hughes: So, Seeburg was as interested in joining you as you were in having him give you some of the technology that he had developed? It was very much a synergism?

Crea: I believe so, because, again, we had showed the world that we could move very quickly with the synthetic DNA and with the gene expression. We had all the tools to do it by chemical synthesis. At that time, the chemical synthesis of human growth hormone would have been a very challenging business because the protein is a very long one; it is one hundred and eighty-one amino acids, I believe. The insulin gene (A and B) all together coded for fifty-one amino acids. So there was a three- to four-fold difference. It would have been at least a year, a year-and-a-half work in the chemistry department alone. We felt that there was no need to wait that long if we could patch the natural gene together with the synthetic DNA and complete the sequence of the gene and of course, the other elements necessary for the expression of the gene in *E.coli*.

Hughes: How confident were you that a patched gene would actually have biological function?

Crea: Well, the insulin experiment was a very compelling one. The gene that was used for the production of human protein in bacteria wasn't a human gene; it was a man-made gene that we designed ex novo from information that we found in the literature on usage of codons in viruses and *E. coli*. So it was clear that we could trick the bacteria by giving them a blueprint which is easily readable by the bacteria because bacteria don't really mind what they are going to assemble. It is almost a mechanical assembly. Once you have created the right blueprint, you can produce almost anything, unless the protein produced is toxic to the bacteria. But at that time, we didn't believe that human growth hormone or any other human protein could be intrinsically toxic to bacteria. It was a good guess to embark on this project with the idea that what was missing from the isolation of a gene from human tissues could eventually be replaced by synthetic DNA.

Now I am trying to recollect exactly this set of events. I believe that soon after we completed the gene, we tried to express for the first time human growth hormone. We noticed that the production of the protein was not very good. We couldn't explain why we couldn't see much of the protein from bacteria on gel chromatography. We got together to discuss which problem could account for the poor expression yields of the human growth hormone. There was a suggestion—I don't remember now who made that suggestion—to refashion the front part of the gene to be more readable by the bacteria. In particular, one of the codons used was a very rare codon which is seldom used by *E. coli*. It was almost like a break in the translation of the DNA. That was an excellent guess, because as we changed that codon into a codon preferred by the bacteria, the yields went up tremendously, by orders of magnitude. So, it was clear at that time that there were some specific requirements to get the best out of the *E. coli* machinery in terms of manufacturing proteins.

Hughes: How intensely were you and others working by '79? You had been there roughly a year.

Crea: In the early months at Genentech we had probably a dozen people, not more that two dozen. So, it was a very small group. It was almost a second family for all of us, and we were all young and energetic. It was more a personal challenge to give the best to make this company succeed.

Hughes: Was there also a little competition amongst the scientists? The cloners didn't want to fall behind the chemical synthesis people?

Crea: I wouldn't say that it was a competition. It was more a mutual pressure; we were putting pressure on each other. Then on top of it, Bob Swanson was putting pressure on all of us. Among the scientists, there was no competition because there was an awareness of complementarity of skills. I wasn't trying to get into molecular biology and vice versa; nobody was trying to do the chemistry. It really was a team effort. It was almost playing together, a major challenge where everybody was asked to produce at his best. In that respect, there was no clock. We were working essentially from morning to evening to try to get to the endpoint of specific assignments as quickly as possible. The rest was good execution, good people around, good teaching, good practices of methodology. Every time you start something in a brand-new laboratory, you need to almost debug the system. Things don't always work as you want. Every time there was a new goal, a new project, it was an opportunity for us to try to do better, faster, and more efficiently. That was, for sure, the work in the chemistry laboratory.

The chemistry that we developed at City of Hope, and then at the early stage at Genentech, was called solution chemistry. In other words, we were doing the assembly of blocks in solution. As we started working at Genentech, one of my goals was to expedite the synthesis. I came up with the idea of doing it by solid-phase synthesis where you attach the first base to the solid support. Then you build the chain on a solid support, and that would give you some advantages in terms of purification and additional synthetic steps. The solid phase was the next goal for the chemistry department with the intention of putting together technology that could be eventually automated by machine, by instrumentation. So we never did routine work. Every time it was trying something different and new to do better and faster.

Hughes: Where had you gotten the idea for fixing the molecules? Solid-state means, you immobilize them on some kind of surface? Was that a principle of chemistry that you had adapted?

Crea: Well, actually, it was the training I did in Holland. In Holland, I started a project for the European Community to immobilize molecules on a solid support. I was very successful using cellulose out of the box and attaching complicated molecules to cellulose. One of the first works that I published as Genentech director of DNA chemistry was indeed a chemical synthesis of DNA on cellulose. Cellulose was a particularly easy-to-handle material. The paper I'm referring to I published with Thomas Horn in *Nucleic Acids Research*,[1] and that paper was also presented at an international symposium in Hamburg in 1979. That paper had the title of "Synthesis of Oligonucleotides on Solid Support Cellulose."

I was looking at the experience that I had before I joined City of Hope and Genentech, and tried to combine the good things that I learned early on with the new challenges. At Genentech, we used cellulose for a number of years in making synthetic DNA. I believe that there was a patent application. Ultimately we realized that there were other polymers that could function as a cellulose. But at that time it was a novelty because we could grow

1.See Crea bibliography, 318, in the appendix of this volume.

a synthetic chain on a solid support very easily and then release the oligonucleotides from it and obtain DNA for gene assembly or other experiments.

Hughes: Were the other DNA synthesis labs, such as Narang's or Khorana's, adopting and adapting this solid-state approach?

Crea: Yes, but, in particular there were no successes around the world, because in effect the big push in the chemistry of DNA happened during those years, when everybody started realizing that DNA synthesis is as powerful as any other molecular biology tool, if you want to build genes. So, the big rush in DNA chemistry occurred after we published the synthetic DNA for human insulin. I remember laboratories in Colorado and other laboratories in the United States were doing some basic work. But the big pressure of taking that basic chemistry, that basic knowledge, into applications, namely, turning that basic chemistry into molecules that you can use in bacteria to produce protein, really occurred after human insulin was expressed in bacteria via a synthetic gene. So, what we saw in 1979 and then later on, was a flurry of activities in laboratories to improve, expedite, modify, and develop new tools, including the gene machine.

From my lab's point of view it was, let's not defocus from the job that we have here at Genentech. Let's not try to chase everything that might be perceived as an improvement, because our chemistry works and can support the current effort, which now is becoming more centered around the molecular biology. I didn't want to change too much. It was more like, let's produce, let's get there first, and then maybe we'll have the time and the financial latitude to play fancy chemistry.

Hughes: That is interesting, because someone mentioned to me that Cetus in his opinion wasted time in developing the technology. In this case I guess he was referring to recombinant DNA technology. The approach he described for Genentech was that they went after products. I suppose that implies that if Genentech needed to improve the technology, then it would, but only in the context of getting the product out.

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Crea: Genentech was more pragmatic—go get it; be there first; we have to beat everybody else. This message was constantly repeated by Bob, who was coming into the laboratories often, talking to the scientists to monitor progress. He wanted to get there first. It was a very sound strategy, a very understandable philosophy. We were small, undercapitalized, and relatively unknown to the world. We had to perform better than anybody else to gain legitimacy in the new industry. Once we did, we wanted to maintain that leadership.

In 1979, 1980, it was more, "We are the only one or the best one in the business; what we can do is almost unlimited. Let's go and be smart in selecting the targets and try to beat everybody else." Nobody had the set of skills and set of tools that Genentech had assembled in the first year or two.

Hughes: Did Cetus ever feel like a formidable competitor? They were already up and running in 1971. So they had a bit of a lead.

Crea: Cetus was always perceived as one of our competitors, if nothing else for their close proximity. If nothing else, we could feel the pressure from the other side of the bay, and

the sense was that Cetus had the financial latitude to beat us. They were a lot better capitalized; they had more money, more scientists. We didn't have that luxury. We only had the luxury to compete from a skill set and our ambition to be the best with less financial means and perhaps fewer human resources than Cetus. Bob used Cetus and Dr. Peter Farley, the president of Cetus, as the threat coming from the other side of the bay to motivate the scientists at Genentech. The other major competitor, although distant, was the group of Wally Gilbert, Biogen, and their European connection with the University of Heidelberg in Germany and Basel in Switzerland.

Hughes: What was the connection with Heidelberg University?

Crea: There was a group of well-known scientists in Germany who were joining Wally Gilbert.

Hughes: Oh, that was the Biogen connection?

Crea: Yes, there were scientists from Germany, from Belgium, and from Switzerland, joining the Biogen effort. It was definitely a very skilled group of people. It was always a fact that they could come up with the next breakthrough before we did.

Hughes: Were you as a group monitoring the literature?

Crea: All the time. Not only the literature, but we were very sensitive and intent to what was disclosed at symposiums and international meetings. It was having our antennae up almost all of the time to gather information. A fascinating thing occurred when we were trying to gather intelligence from competitor groups. It became apparent at the symposium on interferon, which I believed occurred in 1980. Everybody was in a race of isolating interferon and getting a partial sequence, because a partial amino acid sequence would have given out the clue how to go back and synthesize DNA probes and attempt the isolation of the whole gene. Genentech didn't have any information yet on interferon. Genentech didn't have any leadership in the interferon race at the time that we decided to move into the interferon field. We had a tremendous capacity to clone, to isolate DNA from cells, and a great capacity to design and synthesize probes, but we didn't have any depth in the interferon field. The whole race was won when a scientist from Genentech attended a meeting, and he copied down the first four amino acids of fibroblast interferon which were flashed on a screen by one of the scientists who was working in interferon in Japan. With that information, we were immediately jumping ahead of the competition, because we were immediately synthesizing the DNA and giving the molecular biologists the unique tools to go out and fish out the gene.

Hughes: Was that a slip on the part of the presenting scientist?

Crea: In retrospect, the presenting scientist will probably never forgive himself. But at that time nobody really had perceived the powerful technology machinery that we had put together at Genentech. It wasn't until later that it became apparent that a small piece of information—but crucial piece of information—can start a snowball effect if you have the technology to turn that bit of information into a unique strategy that nobody else can adopt. So that will give you an unfair advantage with respect to the competition. We played that very well. That's why Genentech was able to accomplish so much in the first few years of its activity.

Hughes: So, going to meetings and symposia was an important part of the job?

Crea: It was. It was as important as anything else. Again, having in a company a couple dozen scientists with diversified skills didn't mean that we had the depth to be the experts in every field that we were getting involved in. Actually, it wasn't realistic to expect that such a group of skilled people could be also the key scientists in different disciplines, such as virology, immunology, et cetera. It was impossible. So, for us, it was either use the tools for achieving the synthesis and expression of the protein and then dig into the biology and the more medical aspect by working with experts in the field, or looking for the experts, like Peter Seeburg and Axel Ullrich, and try and attract them to Genentech so that they could bring not only the skill set but also the expertise that they accumulated in many years of work.

Hughes: Now, those two—and originally John Shine was supposed to come as well—didn't say "Yes" immediately to Swanson's offer. Do you remember that being a concern?

Crea: Again, we were not surprised by this set of events. Number one, because we knew that the people we were trying to attract were leaders in the field. We knew that people like Axel Ullrich and Seeburg and others had many options to evaluate, not only in academia but also in other companies, in a competitive situation. So, I wasn't surprised that there wasn't an immediate enthusiastic response. It was part of the growing pains of getting the best and making room for these prima donnas to move in with necessary support. The company on the other side couldn't support exponential growth. It wasn't realistic to grow double or triple the number of people in a very short time. It was part of the anticipated growing stage that some people would join early on; some people would take some time; some people would even join and leave the company. In my case, I had people who didn't want to join and people who joined the company and turned out to be not the right people, or they couldn't stand the pressure. The important thing was that we had a very aggressive recruiting policy.

Hughes: Who was largely responsible for the recruiting? Anybody who had a connection?

Crea: There is no doubt in my mind that all of the push was coming from Bob Swanson, and whether there was an influence by Boyer and Perkins, I would say most likely. Really, the true vision was still coming from Swanson and some of the early scientists in trying to anticipate the additional requirements the company had as we were building from the ground up. Bob Swanson was connected with MIT, and he had several consultants aboard from MIT. Also, early on, the company hired some specific people in human resources to facilitate the screening of resumes coming from all over the country of scientists who wanted to join the company. We had ads also in magazines like *Science* and *Nature*. As I said, Genentech was in the press almost on a monthly basis, if not on a weekly basis. We were really building our reputation by very qualified scientific papers, participation in meetings and symposia, by promotion through magazine articles written by science writers, analyst reports. So, there was really a slew of printed information on Genentech. It was quickly becoming a reference point in the scientific world for a number of scientists that wanted to come to the El Dorado of science in joining Genentech.

Hughes: By the time you had arrived in the fall of 1978, was there a publication policy in place?

Crea: Yes, there was a publication policy always in place from the early days of City of Hope, as far as I remember. The policy was that we should publish as if we were in academia, with only the provision that if what we were going to publish represented intellectual property, we wanted to make sure that we first filed for patent. Then we disclosed the information to the public. That was the only requirement—that we get the release by the key scientific staff and the legal department before we published a paper.

Hughes: Would that mean that a Tom Kiley, for example, would review drafts of papers destined for publication?

Crea: Yes, and sign a release.

Hughes: Might he suggest that certain things be omitted or stated differently?

Crea: No doubt about it. But more than anything else, he would look at the content from an intellectual property perspective. If there was something that we didn't include in the patent, or even if we didn't file for a patent, he would make sure that all the proprietary information would be the object of patent application prior to public disclosure.

Hughes: What about presentations?

Crea: Also, we had an internal committee to sign on presentations and publications because, as I said, we wanted to keep the quality of the publications really high. So the scientists were reviewing the papers and signing off on the quality of the science. The legal department would review the paper and sign off on the protection of intellectual property. It was a good system that I think is very much adopted by the biotech industry. The quality of the publications was key for attracting good scientists into Genentech. The fact that we published in *Nature* and *Science* and *PNAS* [*Proceedings of the National Academy of Sciences*], the most prestigious journals in the world, was already a sign that we weren't going to compromise or cut corners with the quality of the science.

Hughes: Did you feel that the paper that came out was comparable to what your experience had been in academia?

Crea: No doubt about it, even better. Again, the people who were writing papers were the same people that were writing papers in academia. There was no limitation on the amount of details to support an experiment. On the other side, we had to prove to the reviewers that we were telling the truth. Eventually we had to provide even more details than anybody else because we were breaking new ground, and as such we were the first to crack certain experiments, certain techniques. So we had to be very detailed.

Hughes: Do you think that it made any difference to the reviewers that the authors came from industry? Would, perhaps, their standard for approval have been any higher?

Crea: I don't think so. I don't think that there was a different way of looking at the publications by the referees or reviewers. I believe that there could have been, in some case, referees who argued, and sometimes even rejected our papers, based on a wrong perspective. For sure, in my case, it happened a couple of times.

Hughes: Did it?

Crea: Yes, I was very annoyed by reading the comments on some of the publications produced. I thought at that time some were completely off the wall, and I couldn't understand whether it was professional jealousy or people didn't understand what we were trying to do. I can't specifically say if it was related to the fact that we were working for a private company or more of the same game that is played whether you are in industry or academia. My feeling is the latter. You always compete with the referees one way or the another. You have to go the extra yard sometimes to explain or convince that what you have produced is valid and of high quality and has to be published. Therefore their criticism is not appropriate.

Hughes: All right, a little bit now about the business aspect. I understand that was not your sphere, particularly. But in a small company you must have had some awareness. Putting it simplistically, is it accurate to describe the three phases of Genentech's earliest business development as, one, contract research and development, two, licensing products to other companies, and three, a FIPCO [Fully Integrated Pharmaceutical Company], aiming to produce every step of the production process within Genentech?

Crea: Well, from a business standpoint, the events at Genentech, as in any other small company, were dictated mainly by the ability of raising money. Your bank account allows you to step on the gas or slow down. What you have in mind is very much sobered by reality, which is that you can't do everything. [laughter]

So, thinking of Genentech and what happened in the early days, after human insulin, the company was very smart to raise private capital. That was a very important milestone. The relationship with Eli Lilly didn't solve the financial needs of Genentech. I believe that it was more a validation that Bob Swanson and the other board members created for the company—validation by a big pharmaceutical company. But in terms of cash flowing into the bank account, it was very modest.

Hughes: Do you mean that the flow was so modest that it didn't necessarily cover the cost of the insulin project?

Crea: I don't know exactly the details, but I wouldn't be surprised, because I learned, secondhand, of course, that there was a $500,000 license fee, and the rest was from milestones and royalties. $500,000 wouldn't even have covered my budget. I imagine that might have been a big struggle in Bob Swanson's mind, because he was probably caught between the urgency to validate the approach that the company had taken and the new technology in this new industry, and at the same time raise enough cash so that he didn't have to dilute all of the investors with venture capital money. So, in retrospect, Eli Lilly was a major event, but the immediate impact was more in public relations than in the financials of the company.

After we had signed with Eli Lilly, there was a successful financing for Genentech in that the company was able to raise money from Lubrizol, which was $10,000,000, something like that, and other private investors. That was our first serious financing. Not only that, but after Eli Lilly embraced the insulin program at Genentech, immediately the doors opened to go talk to other big players like Hoffmann-La Roche and Grünenthal and other pharmaceutical companies. Once we got the money form Lubrizol, the company really started building in a more frenzied way, in anticipation, I assume, of bigger financing through a public offering. It was a groundbreaking event. For the scientists, the message

was clear: the more we continued maintaining leadership in the industry, the more people would be interested in investing in the company. But we scientists very seldom had a role in raising money from private investors. It was more Swanson and Boyer handling that behind the scenes.

Hughes: Was that system all right with you?

Crea: Oh, yes, I was very happy not to get involved in tedious business discussions or even presentations. By then, we had elected a representative on the scientific stuff to play that role, just in case that was necessary. So we had a director of research who was formally in charge of presenting to investors, presenting in meetings, when it came down to selling the science.

Hughes: By the late 1970s, maybe into the eighties, one could deduce that Genentech was following the money. By that I mean, the company's application of these new technologies was in a number of fields—pharmaceuticals, agriculture, vaccines. Was it because of a desperate need for money that wherever you found a company that was willing to support a project Swanson went for it?

Crea: [pause] No, I don't think so.

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Crea: One reason was, Genentech wanted to be accepted as the leader of this new industry; and two, to convince the pharmaceutical industry or any other industry which had business related to biology—food, agriculture—that recombinant DNA was indeed a real technology and not just a fluke. So, even after insulin, after those fifteen minutes of fame, we had to face the reality that not everybody was jumping up and down, saluting this as the birth of a new industry. Everybody was kind of skeptical about the potential of the industry. For sure, the challenge was, "Well, you did this [insulin], maybe you got lucky. But show me what you can do next." I am not surprised.

But maybe that's the nature of the beast when you come up with something fundamentally and profoundly revolutionary. Everybody could dream about the incredible number of applications. Early on, it wasn't difficult to imagine what one could do: plants that don't need fertilizers, cars that doesn't need gasoline, because now we have the bugs—bacteria producing products. You can extend the application in an almost unlimited fashion. The reality was that everyboby was asking, "What is it that is going to be a blockbuster? What is it that is going to turn Genentech and the industry into something real that the investor will believe?" It wasn't easy because initially the applications of biotechnology were essentially focused on producing proteins, not on curing cancer or changing the make-up of malignant cells and things like that. Ninety-nine percent of the foreseeable applications of biotechnology were proteins which could now be produced in bacteria. The perceived limitation was, maybe there will only be a subset of proteins that can be produced in this way because other proteins will be so complicated; other proteins will be glycosylated; the structure of other protein structure will be so difficult from a three-dimensional standpoint that bacteria will never be able to produce them.

Hughes: Well, that became true.

Crea: Yes, that's to say that we were planning ahead in this overall scrutiny and skepticism that this was the answer to the needs of industry and medicine as well. So, in a way, we had to be opportunistic and grab whatever we could to support the growth of the company to take the technology to the next stage of maturation, the next stage of demonstration. I think that it worked out well that Genentech found a group of private investors who decided to invest in the company, and give the company those two or three years of financial latitude to build upon its skill set and produce a number of interesting proteins for commercialization.

One of the happy choices that the company made early on was the selection of human growth hormone. I think that that was no doubt a home run. But initially we didn't have a sense of the business for human growth hormone. As a matter of fact we were looking at bovine growth hormone as a moneymaker, because bovine growth hormone would have had an application in cattle, meat, and milk production. We didn't know how extensively human growth hormone would be used in medicine.

Hughes: Without the prospect of making bovine growth hormone, would the whole growth hormone project never have seen the light of day? It wasn't particularly obvious that the market was going to be very big for human growth hormone.

Crea: You are absolutely right. There was a big push in finding proteins that could be sold to the market, and it wasn't human growth hormone that was going to generate millions and millions. So bovine growth hormone played for a while the role of driving focus and effort for commercialization. It came later that human growth hormone became so important. But I don't want to say that if it wasn't for bovine growth hormone, we didn't have a human growth hormone, because human growth hormone was one of the most characterized human proteins in biology and physiology. So there was a lot of interest from a biology point of view or medical point of view to understand the role of growth hormone in diseases, in maintaining healthy growth, just for overall metabolism, cellular metabolism.‘

Hughes: Was that body of knowledge in place by the late seventies?

Crea: Yes, there was a lot of interest around the function of the hypothalamus, the pituitary gland. Let's not forget that already there was at least one company, in Europe, which was selling human growth hormone for medical application. That was Serono.

Hughes: Wasn't Kabi also?

Crea: Kabi was also another one. These companies were purifying the hormone from the glands of dead people. We didn't know in detail how big the market was going to be. But for Genentech at that time, it was sufficient to identify proteins for which the industry had an interest—maybe a mature interest like in the case of insulin, or an incipient interest like Serono and Kabi for human growth hormone. A lot of science was already known about the hormonal pathways. But the struggle was having a sufficient amount of pure material to develop medical applications, and that was the way I think that Genentech, in the early phase, played an important role.

Hughes: How aware were you all during these early years that Genentech was a model for how new cutting-edge technology could be applied? Was there any realization that you were setting precedents?

Crea: No doubt that we were all aware that we were a cutting-edge company from a technology standpoint. That was beyond question. What wasn't clear was whether the company was going to fulfill its vision of becoming a fully integrated pharmaceutical company. That was a new language for scientists.

Hughes: I bet.

Crea: And when Swanson and the board started positioning Genentech to become a pharmaceutical company, I must confess not everyone was jumping up and down, because we didn't know the implications.

Hughes: Do you think it was a bit premature to be doing that?

Crea: I thought that it was ambitious, but what did we have to lose? From our standpoint, the fact that we had a leader, Bob Swanson, setting up new precedents and conveying the big vision of becoming a big player in the industry was okay. It was confirming that we had produced such an incredible set of discoveries that eventually could support the growth of a pharmaceutical company. But nobody, including probably Swanson, knew what it meant in detail. We had to go through a number of growing pains in learning what development means. I'm talking about process—scaling up, large-scale production, preclinical and clinical development. Nobody in the organization in the early eighties was talking that language, letting aside whether we had the depth to build.

Hughes: You were getting a little exposure through Eli Lilly. Scale up was largely their responsibility, wasn't it, for obvious reasons: Genentech couldn't do it.

Crea: That is correct. I remember that insulin gave us the first opportunity to even talk internally about manufacturing issues, because it wasn't our job to solve those problems or even deal with those problems. But eventually they became our problems because if you have a sound approach at the cellular level or bacteria level, then it is a lot easier to scale-up. But again, for us it was learning a new language, absorbing a new set of information. With the interferon projects, we started digging into the biology. That was the time we hired Dr. Noel Stebbing, from the U.K. to bring some knowledge of the biology of the molecules that we were pursuing.

Hughes: What was his background?

Crea: He was a scientist trained in the U.K. and he was—I'm blanking right now.

Hughes: He was brought in to cover Genentech's lack of expertise in biology.

Crea: Yes, correct. He was essentially there to fill the gap between manufacturing protein and understanding what the protein does at the cellar level and animal level. He was the first at Genentech who set up collaborations with SRI [Stanford Research Institute] to test some of our proteins in animals and design some animal experiments and then build upon that experience to interface with the pharmaceutical companies. That tells you the degree

of knowledge that the company had or had not. It was a constant looking ahead into the future and trying to understand what was necessary for us to build a pipeline.

Hughes: Did Stebbing do that job well?

Crea: I think that for a while he did. It is difficult in my opinion to judge what Noel did or did not do in the company. For sure he managed to bring a different culture and set up a number of collaborations with outside collaborators to test hypotheses to find out more about the activity, the potency, toxicity mechanism of some of these new proteins. In the end, I know that he left Genentech to go and work for Amgen. He became the VP of research for Amgen. I don't know what motivated him to leave. I think that by that time I was already gone—actually for sure, because I was the first key player to leave the company. There was a tremendous pressure to fit different roles and very often multiple roles for key scientists at Genentech. In that respect, there were people who grew well under that philosophy, and there were people who felt tremendous pressure and sometimes couldn't stand the pressure and they left. As the company grew from a half-a-dozen people to many hundreds of people, communication became an issue and became more problematic among the members of the original team.

In my particular case, I was getting more and more isolated from the downstream development, and even the molecular biology was becoming so diversified and complex that it was difficult to participate with the designers of new experiments. It was becoming more polarized, more under the direction of one or a few people, so the company was in a way growing vertically. The science was also diversifying and becoming more the contribution of many other people coming with a different background. I didn't like it. I felt that we were losing something. But in retrospect, it is part of the company's growing stage. I was getting more and more involved in the bureaucratic aspects of running a department with a dozen people. Very little time for brainstorming and collaborations, a more territorial attitude—things that eventually contributed to identified leaders in specific fields who took advantage—rightly so—of the infrastructure that had been created at Genentech. We became focused more on the specialty rather than the synergy.

Hughes: About what time was this beginning to happen?

Crea: I would say 1981, 1982. I left at the end of 1981, so already in a previous year or two, we experienced a lot of growth. Every time we were adding scientists, it became more difficult to follow everything that was going on in the organization.

Hughes: What about your own field? When did DNA synthesizers come in, and what impact did they have?

Crea: Well, the real breakthrough in the DNA synthesizer came in the mid-eighties. But already in the early eighties, we were working, and other people were working as well, on the gene machine. There was a new chemistry being developed to produce the DNA faster, coming from Marvin Caruthers's lab, in Colorado. It wasn't clear what was profoundly new and what was mimicry. For us, it wasn't smart to switch to something that we didn't know and we didn't control, while we were milking the cow which we knew well and we controlled.

In the end, we saw the birth of a number of companies pursuing synthetic DNA. We saw a sophisticated machine coming to the market and then disappearing. It wasn't just the machine itself; it was more the understanding and the control of the chemistry that was going to be used by a machine. Our group attempted to automate the chemistry in collaboration with Waters Associates, in Massachussets. Waters provided the instrumentation, an HPLC, which was turned into an automatic synthesizer, having that cellulose as a solid support. It was more breaking ground and at the same time we were producing quite a bit to support the effort in molecular biology. Ultimately, the DNA machine became a real opportunity for companies. As I said, it became an alternative to the manual synthesis in the laboratory only in the mid- to late eighties. From my standpoint, it was keeping an eye on the progress in chemistry, but at the same time trying to focus on the applications that we could pursue by having at our disposal so much synthetic DNA.

That coincided with the beginning of my uneasiness with the company. I wasn't any longer excited about playing the number game—how many oligos could you produce in a week? That was something that could only go up in time. I was interested in all of the interesting new concepts that were being developed with the use of DNA. For instance, the strength of promotors, the interaction between DNA and enzymes. These are all issues and projects that ultimately turned out to be very important from the manufacturing standpoint. I was intrigued by them. I can make DNA. I can write biochemical software. What can I do with this ability to write molecular software in terms of learning how to play more efficiently with bacteria or human cells or other cells? My interest started shifting from the pure assembly of genes to the use of DNA for molecular biology. Little by little, in our laboratory we were not only synthesizing the DNA; we were also making genes; we were cloning genes. So the definition of chemistry was becoming more and more gray, at least in my mind. But that wasn't easy to be accepted by the other prima donnas.

Hughes: Because they felt that you were encroaching on their territory?

Crea: Exactly. They felt a little bit intimidated or threatened. So, in the end, it was if I can't do interesting work, I am not interested in doing routine; we can pass it on to somebody else. Maybe I can go out and start developing my own systems. We at Genentech were one of the leaders in DNA synthesis in the world. We could introduce restriction enzyme sequences in your genes. We could design new sequences for promotors. We could make all protein analogs by just mutagenesis. We could make artificial proteins, like mini-proinsulin. These are all things that we did at Genentech probably for the first time. We were opening up a world of applications, without going too far from what we were doing every day, just by designing smart sequences.

Hughes: Were these extensions supported by the company?

Crea: To some extent, yes; to some extent they were perceived as being molecular biology territory and none of my business. I worked with Peter Seeburg and a number of molecular biologists at Genentech for optimizing a sequencing system in *E. coli*. I worked with Herman DeBoer on developing new promotors for better translation of messenger RNA. I worked with other scientists in designing protein analogs for better performance, better activity, and even protein engineering. Really, I was smelling and enjoying the flavor of the DNA applications. I didn't feel comfortable any longer being

left at the periphery of that excitement. The more I wanted to participate, the more I was finding resistance by the so-called molecular biologists. So, in the end, I felt uneasy, and I started dreaming of my own organization. That was the time I started thinking about going out and leveraging upon my skills to help many other laboratories to get synthetic DNA. I had a very good perception of how the increasing demand in the new industry was going to support my business in synthetic DNA. In the last couple of years at Genentech, I was working with dozens of outside laboratories in basic research. I was providing primers and probes for interesting projects. I felt that as the synthetic DNA gene machine was moving into the laboratory and therefore the DNA would become available to many other laboratories, that I could facilitate that stage of development, knowing that many laboratories in academia and industry were interested in the synthetic DNA approach.

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Crea: At Genentech, we had DNA chemistry, of which I was director; molecular biology, which I think was either Goeddel or Herb Heyneker; then we had protein chemistry and biochemistry, of which Mike Ross was the director; then we had biology, of which Noel Stebbing was the director. We had elected Giuseppe Miozzari to represent all the departments early on, as a scientific director, but Giuseppe left to join Ciba-Geigy some time in 1980 or 1981. That role—I don't remember—was filled by Dennis Kleid or Herb Heyneker. But when I left in October of 1981, I think the company was recruiting a scientific director, who eventually was David Martin.

Hughes: We skipped over the IPO, and I am curious as to how much this was a discussion point. Was it something that Swanson was preparing you scientists for, or did he consider it his own business domain and managed it in isolation?

Crea: It became clear once the company started raising money from private companies, from private investors, that the stock now had a value. As a matter of fact, part of that private transaction which brought Genentech millions of dollars from Lubrizol, I remember, gave the scientists the possibility of liquidating some of their shares. Specifically, we were told that we could sell up to ten percent of our holdings. For us, it was the first time that a piece of paper was worth something. Some of us did. I believe at that time, the price per share must have been something like three dollars. For us it was good money, because you could put down a mortgage for buying a new house or a new car.

It became clear at that point that the Company's shares eventually were a tangible asset for the early players and the new players. So, we started paying more attention to the analysts' review of Genentech. I remember very well that when the company put together the first annual report—the beautiful brochure in black and white with beautiful pictures—we had the perception that now we were getting ready for the public; we were getting ready for the masses, the large audience. The annual report, dated 1980, featured the company as unique in terms of people, accomplishments, milestones, and the organization as well. It was presented as a very well-balanced organization to sustain growth to become a pharmaceutical company. It was a clear message to the investment community that we were growing by putting together integrated skills and this new set of scientific information and looking forward at the end result of becoming a real business. 1980 was a clear milestone year for the company in that we were presented as a mature organization ready to take off and become an integrated and successful business.

Hughes: Did you have any anticipation of the actual success of that IPO?

Crea: No, I don't think anybody was expecting it. The whole motion wasn't something that the scientists got involved in; it was more Swanson's orchestration. If you would have taken a snapshot at Genentech, you would have found that in the early eighties, everybody was busy building his own kingdom—a good positive aspect. There were a lot of races for new molecules, exciting molecules—interferons, proteolytic enzymes for blood, et cetera. Now the race was for making drugs to save lives, not just for replacing proteins that cannot easily be produced by an animal or by synthesis. The focus was more on, "We can do something to save lives, such as curing heart attack, having an impact on thrombolytic therapy, cancer." So really the motivation was now to build on the science and add depth to the work that we had done early on. The business side was not our problem; we trusted that we have a good management team; Bob was very good at negotiating things; eventually we will succeed. But really, the lack of any business experience among the scientists did not give us the perception of what was going to happen with an IPO. We couldn't possibly imagine that on the first day of trading Genentech stock was going to jump to $89 from $35. Yes, we were curious, anxious to see whether we were going to succeed in getting public support, but not even in our wildest expectations—we anticipated that glorious splash in Wall Street.

Hughes: Do you think that Swanson had any inkling?

Crea: No, I don't think so. I don't think that anybody had that perception. One thing that I remember was that the price of the shares was negotiated until the very last day, and I'm sure that Swanson was happy to get $35 a share. If he knew that the stock was going to ninety, I'm sure that he would have negotiated to at least fifty. It was very much a surprise to everybody. It was a happy surprise.

Hughes: Do you remember exactly how you learned and where you were?

Crea: Yes, I remember there were moments of celebration, but it wasn't the same as the ones that followed the human insulin experiment; it wasn't as genuine. It was more "Wow, now we have become not only well known but also rich." It was a strange feeling, I must say. On one side, of course, we were very ecstatic of the acceptance we had from the public offering. But on the other side—maybe it is part of human nature—I knew that my stock was worth X, but my colleague who was smarter than me and had more shares, now had twice as much. And why? Wasn't I as important as the next guy? So it really started getting into your mind from a different point, from the greedy financial point. Then you start thinking "What alternatives do I have now that I have some financial latitude?" So, it is really a different dynamic that suddenly you're worth a lot of money, and you don't know whether your fortune it is going to go up or go down. It triggers a new series of questions and anxious feelings.

I remember that I was coming back from a trip the day when the company went public. I'm not positive, but it could have been a trip to Los Angeles with Fred Middleton. We were walking in the terminal of the San Francisco Airport and we saw the front page of the *San Francisco Chronicle* with "Genentech," a big title. I was like,"Woo, something happened today." We bought the newspaper and it was a beautiful article—I believe it was the afternoon edition—which saluted the incredible financial exploit by Genentech

on Wall Street. I bought a number of copies, because that was going to be a memento to keep forever.

Hughes: So your new status as a public company didn't change your day-to-day activities?

Crea: No, it didn't because although we had stock it wasn't clear whether we could sell it. It wasn't clear what were the restrictions. It wasn't an immediate money-in-the-pocket situation. It was more a perception that we had built something valuable, that a lot of people were finding themselves very wealthy, and that this was getting to be serious stuff.

Hughes: What about in terms of accountability? Was there any change in that regard?

Crea: No, because the administrative and financial machinery was well in place at Genentech to provide the information required by SEC [Securities and Exchange Commission] filing, investors' relationship, public relations. The company had a number of skilled experts in-house to deal with our new situation. What changed was the frequency of articles on Genentech. There was a lot more interest in the company after that big splash. We saw more and more articles by financial institutions, by analysts, by magazines like *Business Week*, not just *Science* and *Nature*, et cetera. We also enjoyed being at the center of the financial world. There were a number of articles published on the scientists as the players. So that was a good reflection of what had changed.

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[Interview 5: November 11, 2002] ##

Hughes: Today we'll discuss thymosin. This is one of the many projects at Genentech on which you worked. Do you know something about the origins of the project?

Crea: Yes. Whatever I remember after twenty-plus years. Thymosin was our first project at Genentech where we tried to take advantage of an early discovery in biology to mass-produce a very interesting protein. The thymosin alpha-1 was a protein which had been discovered and studied by Dr. Goldstein—Alan Goldstein, if I remember well.

Hughes: Yes, that's right.

Crea: We managed the project together with my colleagues at Genentech, especially Ron Wetzel, who came from the laboratory of Dr. Dieter Söll to join my group in 1979. We approached the scientific aspects of producing thymosin alpha-1 with the benefit of the support of Dr. Goldstein. He came to Genentech to tell us about this important discovery.

Hughes: You mean he initiated the contact?

Crea: He initiated the contact with the group. By then the biology of thymosin was being uncovered, and there were a lot of good data indicating it might be an important protein for mediating the immune system. [tape interruption]

This was an ideal project for us in that the protein wasn't that large—only around thirty amino acids, I believe. Therefore it was very approachable by our synthetic DNA method, which had been successfully used for human insulin and other small proteins. So we decided to embark on this project, and we started the design of the gene.

The early part of the project landed in my laboratory, and my people synthesized the oligonucleotides which were necessary to get this job done. Again, the fact that Dr. Wetzel was in my group and that he was coming from a laboratory where they had done a lot of protein biochemistry was very important; our group had the chance not only to produce the protein itself, but to purify and isolate and start verifying the biology and the biological activity. So it was a good match and gave us also an opportunity to expand outside the chemistry itself.

Hughes: Ron Wetzel eventually has his own laboratory doesn't he? Doesn't he become the protein chemistry expert as opposed to an expert in DNA synthesis?

Crea: Yes, eventually; I think thymosin was indeed the opportunity for him to be at the interface between our group and the protein biochemistry group. From that point on, he did such a great job in taking the project throughout the synthetic steps and the cloning, which was done by the molecular biology group, but he was supervising that activity.

Then he was leading the effort in protein purification, characterization; and he was maintaining the relationship with Dr. Goldstein in studying the biological activity of the recombinant protein. That became an important role for Ron as a project leader. We were successful in completing that project, and Ron did a masterful job in taking the project

from A to Z. In that respect people started appreciating his role as a protein biochemist. As the company started adding projects and people, and the biochemistry became an essential step in the development of recombinant proteins, Ron was given the responsibility to lead his own small group.

Hughes: Do you remember when that might have been?

Crea: I think it was around 1980-81. It was interesting because my group in DNA synthesis was involved with a more and more streamlined process. We had now optimized the synthesis and purification, so really the synthesis of oligonucleotides, per se, was becoming routine—to the extent that people could use DNA by simply filling out a form, passing it to my people, and getting the DNA ready within a week or two. In that respect, it was a lot more interesting to apply the use of synthetic DNA to interesting projects where the end point was either an improvement in molecular biology—a new discovery in molecular biology—or all the way through the protein expression and characterization.

I felt, myself, that having optimized the chemistry and having built the group, that it was working sufficiently to support a very large number of projects. At Genentech, I was losing a little bit of track of what was going on downstream because the use of DNA quickly branched into all kinds of projects at Genentech. There was a use of probes for fishing out messenger RNA: a use of primers for mutagenesis or for isolation of messenger RNA or cDNA synthesis; there were synthetic genes; or other use of DNA for modification of genetic elements, like promotors, terminators for plasmid construction, and expression improvements.

So the DNA was readily available. Why not use it for everything, to take a lead in the industry? In effect, I was extremely pleased by this fact that our group was supporting the entire organization, but on the other side, I was becoming aware that I had to do something new and different. Otherwise the risk of being a turn-key department would have been very big, and Ron Wetzel, also, as an intelligent scientist, felt that his role in the company could be more rewarding if he would take more responsibility for the characterization of the protein. With Ron Wetzel, obviously Genentech was able also to introduce some additional techniques and technologies as well. At that time the computer modeling of proteins became an important tool for understanding the structure of protein and trying to correlate structure to function. So in that respect, Ron was capable of establishing relationships with leading groups in academia, such as UCSF, and bringing into Genentech that modeling capacity.

With respect to my own interests, I had already branched into other activities for chemistry. We were doing a number of additional projects which went beyond the improvements of DNA chemistry as such. For instance, I was working in collaboration with a group in Holland to study the function of small, modified nucleosides in the activation of the interferon alpha expression. I was working with Dr. Noel Stebbing, head of biology at Genentech, to develop some nucleoside and nucleotide analogs as supposed anti-viral compounds. So we were already ahead with some interesting projects for small molecules based on the DNA chemistry.

Hughes: Was this enough to keep you happy?

Crea: To some extent it was, in that I had a number of projects to pursue on my own, but on the other side, I was too interested in the molecular biology, cell biology revolution. I was at the very head of that revolutionary process. To some extent my group triggered the unfolding of that revolution, and I was extremely excited about participating, especially in the protein engineering in the designing of gene analogs, which could eventually lead to protein analogs with improved properties. I had a feeling that we had now the "software" readily available to direct bacteria in mammalian cells to produce designed proteins, and that was an open world. It was unfolding, and I wanted to be part of it.

Hughes: Now did it take any particular effort for you and the people you were working with to move from an emphasis on the nucleic acids to becoming protein chemists? You were still chemists, I would think, with a capital "C," but what you were applying your chemistry to began to shift, did it not?

Crea: No, actually it wasn't difficult for people like me to move across projects. Obviously the intention wasn't to replace the so-called "experts."

For instance, in molecular biology, during my period at Genentech, there were tremendous improvements in techniques and technologies. Obviously, you know, I wasn't trying or pretending to replace the skilled molecular biologists in the laboratory. But the big picture was different. The big picture was that you could, in effect, now you had all the tools to program the protein production mechanism in the cell, control that mechanism with bacteria or their cells, to the extent that you could design things in the laboratory and generate a specific protein. It was a lot of power, because now you could think of modification dictated by scientific evidence or intuition or structural-function activity relationship.

So in a way, as a chemist, I could appreciate the function of a protein in its biological activity. In other words, in the end each protein is different because of its structure. So if the activity is due to a structure and you can control the structure and change the structure, obviously it becomes very exciting to understand the fundamental rules of that game and try really to generate an optimum protein with optimal biological activity for a variety of medical and industrial applications So in that respect, it was more a decision how to spend your time in the laboratory, whether to focus on the end point, or on the middle point, or at the very beginning.

I had done my time, and paid my dues at the very beginning with the DNA chemistry. Now I wanted to participate in the really tremendous opportunity that technology at the DNA synthesis and molecular biology level had created for the ultimate output of the protein itself. When you look at the structure of proteins and you look at the interactions between proteins, it comes down to chemical interactions. So that, culturally, was very close to what I was doing with the DNA. It was just shifting focus from DNA to proteins, but from a chemical point of view, the rules are very, very much similar.

Hughes: Well, understandably, we diverted from thymosin. Do you want to say something more about that?

Crea: Well, no. There is another part of my career, which obviously had influence on my shifting from DNA into the proteins.

Early on, we had initiated a parallel project for the synthesis of proinsulin, and mini-proinsulin. That was in 1978. At the same time, we were working to produce the synthetic genes for the A- and B-chains. We were already thinking about a smart, unique modification: how to shorten the length of the C-peptide, which is the peptide that in nature holds the A-chain and B-chain together in a way that they can form disulfide bridges. Then the C-peptide gets cleaved by enzymes, and you get the native insulin. But even as early as 1978, we were talking about artificial modification of the C-peptide to make it long enough to position the two chains (A and B) so that they could form the disulfide bridge without having to go through this long chain that nature has adapted.

So in other words, we were trying to outsmart nature by modifying the size and the length and the structure of a natural component so that artificially now, in bacteria, we could get the same effect but with a much simpler strategy.

Hughes: So that was a refinement of the process, wasn't it? Somatostatin preceded insulin, but that, if I'm right, was just a matter of pasting the somatostatin gene onto a larger molecule. It wasn't that you changed the gene per se.

Crea: Correct.

Hughes: So here you were, for commercial reasons, changing nature's design.

Crea: Correct. Yes, and again, it was scratching the surface of the numerous applications that became immediately available to creative minds having synthetic DNA at their disposal. Now you had a situation where you could impact on the industrial production of a protein by changing, artificially, the length of a peptide. So that was very attractive.

When we started the mini-insulin project, in effect, we were opening up a new world of applications which today is recognized as protein engineering. We were doing protein engineering. Obviously, you know, many laboratories were thinking in a similar fashion. But we were doing it while other people were still thinking about it because we had the tools in hand.

Hughes: Now do you think from the start people had, well, people particularly at Genentech, had the idea that what they would be attempting to do would be more than just duplicate nature?

Crea: Yes, although, from a business standpoint, it was the first strong message that the company was trying to convey to the industry and to the public. Here we are with a new technology capable of reproducing what nature does, in a much easier, much cheaper fashion to pass the benefit to the patients or to the consumers.

So the first message was, "We don't need any more very complex systems to produce large quantities of human insulin for diabetes. We don't need to really harvest hundreds and hundreds of kilos of human pituitary glands from cadavers to produce human growth hormone. We don't need"—to use another example—"We don't need to grow thousands and thousands of liters of media to isolate a little bit of interferon; now we can use bacteria, which do the job in a soup essentially."

Hughes: The point I've taken for granted is that recombinant DNA and the other genetic technologies were going to do things faster or more efficiently than had been done using more traditional techniques. But the idea that hadn't occurred to me before until this conversation is, you don't just duplicate the insulin molecule, you tailor it through an industrial process to make it more efficient, or more productive, or whatever it is. Was that idea always implicit in the biotech endeavor?

Crea: It's fascinating, as things become obvious when you have the tools, and maybe the first time, you don't rationalize, then you do rationalize and because it's so obvious, you don't think that that was the first time. You don't think that you might have been the first in the world.

I think that was, in a way, the origin of protein engineering. In other words, with a synthetic DNA, with the use of probes, early on we demonstrated that you can change a gene very easily. So you can take a natural gene and you can design a complementary piece of DNA with a one-base mismatch to change one codon in your gene, and obviously, by changing one codon, if the codon is responsible for a specific amino acid, once you put the system back into the cell, you're going to get an analog. It was like, "So what? We can do it." It's almost a natural progression.

But in retrospect, you know, that was the birth of a new, powerful technology, which is today recognized as protein engineering. I'm not saying that Genentech invented that; what I'm saying is that what we were doing, we were doing very early. We were the operators. We were thinking and doing much earlier than anybody else.

The insulin was a first example, but when we started working on GIP, the gastrointestinal peptide, there was a clear intention to generate peptide analogs, to identify whether there was one specific peptide that could be more active than a natural one. So that was, again, a specific project to change the structure of peptides to identify something that even nature had evolved, and anticipate that kind of evolution in the laboratory to be able to discover something which works better from a health care application.

We did it. We generated a number of analogs, but very often, when you deal with technologies at an early stage, you stumble into unanticipated, time-consuming steps which might discourage you from taking full advantage of that technology until another piece of technology helps streamline that process. I think that was the reality. In other words, if making genes, and making gene modifications in gene analogs was easy, it wasn't so easy to take the gene into the bacteria and then express and purify the protein in quantity such that you could study very quickly and very easily in the laboratory to say, "Yes, this is a better one." Or, "No, it's not. Let's go back and redo it." Obviously, the tools were there, but the underlying capacity to understand which change in the protein, and why, still remains a big challenge in biotechnology and biology as well. So it is today, twenty-five years after we have developed the tools. So again, the creativity, in a way, often gets tempered by what you can do in the laboratory—by the cost, speed, of going through the motions; if it is very lengthy and expensive, obviously, you can't do it many times.

But, yes, the use of DNA eventually became almost universal for these kinds of studies on proteins. That's where, also, the modeling became important. Having a lot of proteins now available from recombinant DNA, and having the possibility to modify those

proteins—we needed as a community to develop some tools to direct our manipulations, our changes, in a very intelligent fashion, rather than in a random way. The computer modeling was a first attempt to visualize the changes based on mathematical calculations. What happened if you replaced now one amino acid or a few amino acids with others, what happens to the structure of the protein, and what kind information can you gather from that new structure as related to its biological activity?

Hughes: Shall we pick up the thymosin story again? [Laughter]

Crea: Well, the thymosin in my mind is a short-fuse program. We verify that we can do it, we go once more through the motion of making a gene, cloning the gene, producing the proteins—and let the expert isolate the proteins, identify the activity, and then take it to the next step, which was the pre-clinical experience.

As director of DNA chemistry, you can follow your own babies to a certain point and then you have to let other people take over. So for me, it was, "Okay, this is the end of thymosin." We finished our job. Dr. Wetzel is doing a fantastic job in taking it all the way to the laboratory of Dr. Goldstein so that he can verify the biology and ultimately come back to us with some answers: whether or not this protein is ever going to be a therapeutic agent for the benefit of sick people, people with some diseases.

But at that point, things get too far beyond what we do daily, and if you decide to jump on one project, then you lose the opportunity to do the others. So it's always a challenge to prioritize projects in the laboratory.

Hughes: Do you mean by that you believe there could have been therapeutic potential in thymosin if Genentech had chosen to put more emphasis on it?

Crea: No, I think that Genentech as a company had to make some choices based upon business opportunities and technology limitations as well. While we were working on thymosin-alpha 1, the interferons as a class of molecules were being discovered, and there was a lot of excitement around interferons as potential molecules for the cure of cancer. Now they are major drugs for several diseases. I believe when you are in a position to "cherry-pick" your projects, you start developing plans, and often the plans which Genentech did have to keep in-house were several—

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Crea: Some of these—projects at that certain time might not be as valuable. I believe that thymosin was at its early infancy from a biology standpoint. We didn't know too much, and it was difficult to understand the specific activity or the range of activities. So I believe that the decision to prioritize other exciting projects came easy for Genentech.

Hughes: Does that reflect the undeveloped state of immunology around 1980, the late 1970s?

Crea: Yes, no doubt about it. Thymosin might be a good example. We have other examples, for instance, growth factors. We knew that they were important proteins because they were discovered to mediate some important biological mechanisms. But we didn't understand the full importance until years later. We are still digging in to understand the full significance from a physiology standpoint.

So it's true. Very often when you are ahead of your time you are capable of making something, but there is no science that supports the use of a specific molecule or protein to justify the investment of hundreds of millions of dollars in clinical development. If the science doesn't support the development of the protein, you're taking a big risk because you might develop protein as a therapeutic for the wrong application, and then find out that it doesn't work. It doesn't mean that it doesn't work in the body; it means that for that specific application, you won't get any results. But maybe later on the same protein is discovered as an important therapeutic for something else.

Hughes: I believe it was you who said that the importance of introducing into Genentech a stronger biological interest became apparent. I wondered what the thinking was. Swanson perhaps thought, "Well, all I need is chemical synthesis and people who can clone genes."

Crea: I believe that every time a private organization has to depend on somebody else, it puts itself in a very vulnerable position. I think that the thymosin might be just the example of what I'm talking about. We were doing something for an external laboratory, so we didn't have any control. We were providing the protein—the active material—but then it was totally out of our control, totally in the hands of somebody else in another laboratory. Every time you do that, you know, obviously you feel yourself taking a lot of risks because you don't have direct control. I think that might have been one of the reasons that prompted Bob Swanson to establish a stronger biology department.

To the extent that we can understand proteins, their function, their activity internally, and we can verify with our own experiments—animal- or cell-based—the biological if not the pharmacological activity of a protein, then we have total control. Then we can make an intelligent decision whether or not we should go for a cure of cancer, or cure a neurological disease or diabetes type 2, et cetera.

Stebbing was the first at Genentech who established the initial animal study verification in support of some of the projects that that company was pursuing, like interferons for instance, and growth hormone. So it was a way to build the infrastructure of the company such that we could become stronger, independent, fully integrated, and less dependent on other people at other laboratories.

Hughes: So Swanson wasn't difficult? He came around to that idea without much persuasion?

Crea: No, I think it was recognized by everybody at that time that the more we can add internally the better off we are. That in a way is the blueprint for the growth of Genentech. You can see now where Swanson and the board were driving in the early stage. They were trying to identify the downstream disciplines and skills which eventually would be internalized to become more and more a well-rounded business and technological powerhouse; to be self-sufficient and not to be dependent on other companies or other laboratories.

Hughes: Now in the earliest days, my memory is that there were only three people on the board—Swanson, Boyer, and Perkins. Boyer was the only one on the board who knew the science. Did he advise that Genentech needed to acquire biological knowledge within the company?

Crea: I believe that in part came from Boyer, but don't forget that there was a constant dialogue between the scientists and Bob Swanson on the different projects, almost on a daily basis and for sure on a weekly basis. So there was this constant dynamic in understanding what else the project needed in order to achieve success. I believe that the majority of the visionary position came from Bob Swanson—also because he had the luxury to interact with a lot of creative minds who were identifying on a daily basis the next new, important step.

Hughes: Also at some stage certain scientists began to make presentations to the board, did they not?

Crea: Yes, absolutely.

Hughes: Did you ever do that?

Crea: No, I never did it other than very early. I remember I was part of the team, together with Boyer and Swanson, which went to promote the interferon project with Hoffmann-La Roche. But we had a scientist designated to represent all the research departments. I think it was Dr. Miozzari. And it was up to Miozzari to convey to the board the depth of our technology and the range of projects we were pursuing; to keep everybody abreast with the progress.

Hughes: When a board meeting was coming up, do you remember if Miozzari tended to take more note of what the scientists might feel? Would he come around and collect opinions?

Crea: Absolutely. Miozzari was a very intelligent person who had a lot of good chemistry in interacting with all the key scientists. So he was definitely representing not just himself, but the small community of the scientists at Genentech. [tape interruption]

A major resource available to Swanson, to the board, was a range of good consultants with different backgrounds coming to Genentech. Obviously, you know, you hire consultants to hear what's going on out there. What is it the company needs to do well in its projects? What kinds of skills did we need to bring in-house to accomplish that?

Hughes: Do you remember who any of those people were and what they were consulting about?

Crea: I remember one for sure, and that was Professor George M. Whitesides from MIT. He was a great resource to the chemistry department, to the protein biochemistry department. Professor Whitesides is a recognized authority in organic chemistry and protein biochemistry. So I think we got a lot from him. He was—or still is, I guess, MIT emeritus professor, and he was one of the teachers of Swanson in chemistry. He knows extremely well what's going on in the field of science and medicine as well. So I think he was very instrumental early on, but I'm sure that there were a number of consultants. I left the company in 1982, so I imagine that from that time on a number of people came to work as consultants.

Hughes: Well, should we proceed to proinsulin?

Crea: Yes, the proinsulin was an attempt to simplify the downstream assembly of the insulin molecule. You know, insulin is made of two chains, A-chain and B-chain. They need to

align properly in the cell to form a disulfide bridge. There are two intracellular disulfide bridges that require that the two chains come together at a distance where the disulfide bond can be formed.

The reason why we started the proinsulin project came as a result of the technology limitation of making A-chain and B-chain separately in bacteria, and then trying to reconstitute the molecule in vitro. That is a very difficult, time-consuming, and especially inefficient kind of process. The idea was, well, why don't we try to mimic nature and try to do exactly what a human cell does—except we tried to do it in part in bacteria. We provided the enzyme so that the bacteria didn't have to clip the C-chain after the A and B go together.

The proinsulin was, again, taking the A- and B-genes that we synthesized early on, modifying the end of one and the beginning of the other one to fuse the two genes to the C-chain, which was also synthesized chemically, and doing it again, going through the exercise over and over. This time it was a longer gene which included the B-chain, C-chain, and A-chain, in that order, and to express in *E. coli* and purify the precursor and then let the precursor fold outside the cell as it would in the cell. After the refolding is complete, come with an enzyme that clips the C-peptide and restores the insulin.

It's interesting because this project came as a result of our early collaboration with Eli Lilly. Eli Lilly took over the scale-up of the human insulin to produce a commercial product and realized early on that it wouldn't have worked with the B-chain and A-chain separately. We did it at the laboratory level, and the best we did was to produce one milligram of human insulin. But, that was plenty to validate the concept, but it wasn't obviously sufficient—

Hughes: For commercial purposes.

Crea: So a deep analysis of the technology developed at Genentech obviously resulted in going back to the drawing board and redesigning the strategy, which we did.

Hughes: Who was directly involved in the redesign?

Crea: Well the redesign was extremely straightforward because there was really not much of a brain in order to do that. Again, that was a simple situation where we had to reproduce, exactly, the amino acid sequence of human insulin, and modify the 3-prime [3'] end of one gene to accommodate the beginning of another one, and then attach to the second gene, a third one. It was just a simple replacement of DNA to come up with a longer gene. So that was no big deal. There was no new science at that point. It was just redesigning based on a genetic requirement, more than a protein and peptide requirement. So that was a small project.

Hughes: And where does Eli Lilly fit into this? Because as I understand it, they were given two different types of clones? One was with this proinsulin approach, and what else? Weren't there eventually two methods that Eli Lilly was using and then began to favor one over the other?

Crea: Well, I don't know exactly how many constructs were produced. But for sure Eli Lilly became our industrial partner for scaling up, and industrial development of insulin had

the job to mass-produce the protein. So I imagine the scientists that Eli Lilly started with took the clones and bacteria which we had produced in 1978, and produced separately the A-chain and B-chain and tried to assemble that way the human insulin.

What we learned early on—around 1979—was that it wasn't efficient to produce separately A and B. That's when we decided to do the proinsulin, to try a different alternative. I'm sure that having the mini-proinsulin in hand, we might have also given Eli Lilly this alternative construct to try. Again, it was like "Let's build another model and see whether it works." Ultimately, one of them—proinsulin—must have worked because that was the one that was selected by Lilly for scale up. While we were working on other things, one day we learned that insulin was ready to be registered and approved by FDA.

Hughes: That was pretty exciting!

Crea: That was a pretty exciting time. I still keep one of the insulin—called humulin—vials embedded in glass as a memento of the historical moment. It was the first product made by scientists in the laboratory with recombinant DNA technology, which was introduced in the marketplace.

Hughes: Did you have any direct contact with the Lilly people?

Crea: Only at the very beginning. But again, it was more the protein people interacting. Michael Ross was a head of that department, so Mike and his people were the interface with Eli Lilly. That was an interesting situation. I'm sure that a lot of people at Genentech must have shared this sense of letting somebody take the ball and run. We are a team, and each player has a function. I'm defense, somebody's a quarterback, and somebody's in charge for scoring.

It was interesting how the protein people—the protein biochemists—in essence, had the great job of taking the ball, taking the protein ahead, and going ahead to score. Because that excitement of interacting with the ultimate user or manufacture was never shared with people who did the early job. It was more in the hands of the people who would better interface with the scientists of the other company.

Hughes: Was that hard to take?

Crea: Not really, no. To the extent that it didn't become a territorial fight. To the extent that there was an overall recognition that it was a team effort. It became less pleasant as the company grew. You can imagine at Genentech itself maybe thirty people at one time were involved in the same project, but only one or two had the luxury to come back with the glory of having interfaced with the ultimate scientist or company, which made the final breakthrough.

Hughes: And that tended to be the cloners in the early days, did it not?

Crea: In the early days, it was the cloners, because there was a lot of interaction—well, for a number of reasons. The cloning and the expression of certain proteins was still not a trivial task. So being able to be the first to clone and express a protein like interferon, or human growth hormone, or tPA was still a front-page event. Later on when cloning and

expression became almost a routine, obviously, the focus shifted to the biology, to the first experiments to demonstrate that the protein produced in *E. coli* or mammalian cells did indeed something exciting in animals or even in cell systems in the laboratory.

Of course, then later on, the focus shifted to the clinical development. In other words, to the ultimate answer, "Is it going to work in the hospital—to help people who need it?" Or, "It has been a great attempt, but nothing else but a great attempt." So you can see how as the science evolves and the technology matures and becomes readily accessible, you lose the halo of hero. You become a normal mortal. I thought that there was a lot of excitement downstream for proteins and protein engineering—and then to be only a common mortal at Genentech—. [Laughs] So I wanted to do it outside of Genentech; that was one of the reasons I left.

Hughes: Shall we discuss the interferons? The interferons, of course, were in no way discovered by the genetic engineers. There had been various people for many years—

Crea: Many years earlier.

Hughes: —trying to develop them as therapeutic agents. My understanding is that one of the big drawbacks was that they were present in very small amounts. And because they were present in very small amounts, their characterization was not adequate?

Crea: It was very difficult. People detected the presence in the cell of interferons and people knew they were proteins, but they were such a small quantity that isolating even milligrams of these molecules was really a huge undertaking.

Hughes: I read that Kari Cantell, the Finn, who seemed to have the best cell source in the seventies—

Crea: Yes, human blood cells.

Hughes: Leukocytes?

Crea: Leukocytes, yes.

Hughes: —made, with constant effort, a milligram a year.

Crea: From probably hundreds of thousands of liters. That tells you how difficult it was—the task of identifying the chemical structure of these molecules. I think that when that became apparent, the race to identify the gene via messenger RNA and cDNA became an incredible opportunity for biotech. Nobody could in the world reproduce what Professor Cantell in Finland did, but now Genentech and other companies had the tool to attempt to fish out the teeny, teeny amount of messenger RNA which is present in the cell with some new and powerful tools called oligonucleotides—synthetic DNA. And enzymes of course, for the amplification.

Hughes: The hype was, and there was quite a bit of hype even before recombinant DNA got into the picture, about how these interferon molecules were going to be *the* solution to cancer and viral diseases.

Crea: Oh, viral diseases.

Hughes: Why when so little was known about interferon could one leap to that conclusion?

Crea: It was just a lot of interesting hypotheses based on cellular events. But nobody in the world had enough material to test those hypotheses in real life—in animals or even better in humans. So it was like, because of what we see at the cellular base, the activity as an anti-viral, that we imagine that if we had enough of this in our body, we could block the viral activity. So that was really driving the interest. There was no clinical or pre-clinical evidence that these molecules would work.

But among scientists, it was clear that these molecules eventually would play an extremely important role in medicine based on studies and research at the cellular level. That was enough to drive the interest of the pharmaceutical industry, and therefore the interest of biotech companies like Genentech. But just to put things in perspective, we didn't have any internal research on interferons. What we knew was just out of literature or seminars, conferences. But we knew that we had the tools to be the first to fish out extremely important information to be capable then to mass-produce these proteins in the laboratory.

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Crea: Fibroblast interferon, which was our first interferon project at Genentech started from getting sequence information—protein sequence information—at a symposium. So that was the extent of the information that was available with regard to the protein. A scientist in his presentation at the symposium showed some slides with a partial sequence of these proteins, which had been generated from a very teeny amount of interferon in Japan. The scientists at Genentech—literally by phone—communicated back to our laboratory, and from there we were able to build the genetic tools—the DNA probes—which then were used to go and fish out the messenger RNA for a fibroblast.

Hughes: And you literally did that immediately after the phone call?

Crea: On a dime, essentially. Literally on the phone. The time that that slide was flashed on the screen and the time of the telephone call, we were already up and running.

Hughes: The scientist who was listening to the presentation was Herbert Heyneker?

Crea: I believe it was Heyneker and David Goeddel.

Hughes: Amazing story.

Crea: In a way, it tells you a number of things. From a Genentech standpoint, it shows the powerful machinery we had put in place to go from a small amount of information that you can generate from the protein sequence—two, three, four amino acids in a row—to the set of tools that you can put immediately in place to start a very unique and powerful search for that teeny amount of messenger RNA.

Hughes: Right, and it may have been you who told me that Genentech's technological preparedness to dive right in was not known. Otherwise, it's quite likely that the presenting scientist would not have been quite so forthcoming. [Laughs]

Crea: Oh, absolutely. You are absolutely right. It was really outside any imagination that from back east to California in a fraction of a minute you can trigger such a powerful set of experiments out of flashing a slide. That was really the potential that we had built.

Obviously, I would never want to trivialize the work that was necessary to fish out the gene, and sequence the gene, and clone—I mean again, it was amazing how well oiled the machine had become, to start even the most difficult challenge in biotech, but that was the reality. We were in a unique position in the world to take advantage of a teeny piece of information and trigger a series of events to really establish a leadership in the field, which we did.

And we ended up being the first to isolate, clone, and sequence fibroblast interferon. That led to a number of patents for the fibroblast interferon. The second time we tried for leukocyte interferon we had the benefit of working with a powerhouse like Hoffmann-La Roche. A molecular biology group at Hoffmann-La Roche led by Dr. Sidney Pestka provided the information on the protein—the small sequence required to design the DNA probes.

Hughes: That relationship came after fibroblast interferon?

Crea: Yes, the leukocyte was later.

Hughes: Genentech did the fibroblast on its own without the association with Roche?

Crea: Correct. Then we made a deal with Roche only on leukocyte. Also, it's important to understand that it wasn't just a simple go back to the laboratory and synthesize another piece of DNA.

I think we very fortunate to have a library of dimers and trimers, which was built early on at City of Hope for the insulin gene, a portion of which was transferred to Genentech. Because of that library of dimers and trimers, we were able to assemble the DNA probes in a unique fashion, as mixed probes to cover the redundancy of the genetic code. It's an interesting exercise, but you understand that one amino acid doesn't necessarily tell you that there's one codon. There are amino acids for which there are six codons. So we wanted to select an area of the protein where there's the minimum amount of variability. [tape interruption]

Hughes: Did anybody else have the ability to construct probes that would cover the redundancy?

Crea: No, there was nobody else in the world who could produce oligonucleotides to cover quickly the redundancy, other than making individual oligonucleotides. We were already ahead, and we were mixing trimers together so that you could generate two or four oligonucleotides in the same pool. So imagine, out of a stretch of four amino acids, based on the genetic code, you may have a number of different possible DNA sequences. By using mixed trinucleotides to assemble the synthesized oligonucleotides, we were able to cover all the possibilities in subgroups. So now you could work with a subgroup of four

different sequences to narrow down because the hybridization would occur only with a subset. That subset would narrow down the possibility. So it was a very clever way to re-engineer the genetic information backward.

Hughes: Is that immediately what you did when you had the phone call? You made these broad probes?

Crea: Yes, exactly.

Hughes: Had you done that with other projects?

Crea: No, I think that was our first time. I think later on, because of the powerful amino acid sequencing technology—technology which was developed by companies like Applied Biosystems for sequencing of peptides—it became easier to access sequencing information for proteins. But at the time we were working on interferons and other molecules that technology wasn't available. So you needed a lot of material. Later on, it became sufficient to have a fraction of a milligram. But that system eventually became almost a method of choice—to go from protein to oligonucleotide probes for the isolation of messenger RNA.

Hughes: I believe when you first took on the interferon project, it wasn't clear that there was a whole array of interferons. I mean people spoke of interferon.

Crea: Correct.

Hughes: Weren't all of the early biotech companies targeting interferon?

Crea: Correct. To some extent that was true for fibroblast interferon. I think alpha fibroblast was the only species of fibroblast interferon, the predominant species. But for the leukocyte, immediately the scientists at Genentech identified something like eight different species. It was clear that they were two totally different situations.

Hughes: And all of that was unknown when you began?

Crea: It was unknown, yes.

Hughes: Then, so you were all of a sudden faced with not just one beta—I think it became beta interferon, right?—

Crea: Yes, right.

Hughes: —but many. So how does one choose which to develop? Or would it have been possible to develop all of them up to a certain stage?

Crea: It was not so useful information to find out that there were multiple species because obviously now the big dilemma was which one is more important. And still the answer was not quite clear, because obviously each one might have its own function, its own importance. For us, it wasn't just a matter of picking one; it was more a matter of establishing an early patent position to block the competition from jumping on those molecules which were discovered by Genentech.

Hughes: And did you have patent coverage for all eight?

Crea: Yes, I imagine yes—all the sequences and even other sequences that were identified later on. Yes, protein sequence is obviously very important in establishing intellectual property. I'm sure that Genentech did a good job in protecting that.

Hughes: But in the end, Genentech did pick and choose which interferon it actually worked on, did it not?

Crea: Yes. Well, for instance, out of the information that came from the interferon research, some of the biotech companies did select some molecules. Whether it was based on proprietary, intellectual property, and biology, I think there was some early selection. Interferon-alpha, for instance, became a therapeutic drug.

I remember Amgen came up with the idea of consensus interferon, which somehow was the result of combining all the different variants in one molecule which represented the entire community. [tape interruption] Yes, Amgen had a clever way to take a portion from each natural protein to come up with what they thought was the most active molecule. They called it consensus interferon.

Hughes: Did it work therapeutically?

Crea: Yes, it was a molecule which was developed therapeutically.

Hughes: That didn't interfere with the patents?

Crea: No, it's interesting because as you imagine, that was an obvious concept. But as I said before, it becomes obvious after somebody—

Hughes: Does it! [Laughs]

Crea: Does it for the first time. And obviously, nobody did it until Amgen produced that consensus sequence, and they were able to cover that with patents and develop that molecule.

Hughes: What kind of effect did that have on the commercial potential of what Genentech was developing?

Crea: Well for one, it put the Amgen consensus interferon outside the patent umbrella. Very often, that is the name of the game. You might have great molecules, but if somebody has a patent you're not able to use them. Whether the consensus was an expedient to circumvent the patent, or the result of science or scientific observation, it beats me. I think it's most likely the first, because there was no way at that time to understand which portion or which subunit might play a more important role. Again, it could be thought that by having at your disposal many isoforms of the same protein, and having an assay, you're capable of identifying a certain portion of the molecule which plays a more important role, but I'm not aware of any in the system.

Hughes: But the ultimate therapeutic function of these molecules was shifting over time because, as we mentioned earlier, their role as spectacular cancer agents and anti-virals really

didn't pan out. So how can you select portions of molecules for function if you don't know what the function is that you want?

Crea: You're absolutely right, and very often we rely on cell-based assays. In other words, you rely upon the best assay that you have available to make some intelligent selections or choices. I'm sure that at that time, Amgen had cell-based assays to correlate the structure of the different interferons with the activity on the cell.

Hughes: I see, so they did know.

Crea: So they knew, at least from a narrow angle that certain parts of certain proteins might be important to that function. It's cutting and pasting, and I think that sometimes you're lucky, and sometimes you're not. But it could have been also that this exercise of cutting and pasting led to a more active molecule, where activity was essentially determined by a cell assay. They probably decided that if it works better with a cell, ultimately it might work better with human organs.

So you take the risk, and as you said, sometimes it works and sometimes it doesn't. But in retrospect, the interferon research at Genentech is a great example of how the technology wasn't just a tool to provide just the synthesis of protein, but it became itself a tool for discovery. By applying biotechnology to a cellular system, scientists became capable of making brand-new discoveries, which in turn, of course, fed the biotech industry and the production of novel therapeutics.

Hughes: Well, I think we have to wind up, judging from all the phone calls you've been getting.

You left Genentech because you wanted to use the technology that you'd have a large part in developing in more creative ways?

Crea: Absolutely, yes.

Hughes: Why couldn't that happen at Genentech?

Crea: It was becoming territorial. Interference. Genentech had grown from a dozen scientists—even less when I joined, we were only four or five—to a few hundred, with a number of departments, a number of senior people, a number of lead scientists.

Obviously the scientists started branching into a number of projects. For a laboratory like mine, which had played an important role early on but was becoming more and more service oriented, it was very difficult to become more than that without invading other territories, without confronting other scientists and other ways of thinking. So it became clear to me that the range of research that I could pursue was either in chemistry or nothing at all. I wasn't really interested in developing the chemistry; I was more interested in the end result of the beautiful recombinant DNA technology. So I was becoming more and more frustrated by not controlling the outcome of the DNA software I was building in my laboratory. I felt that maybe a small organization outside Genentech where I could have my own people—my own molecular biologists—would give me a lot more latitude.

Also, let's face it, I've never been a large-company person. As Genentech started becoming a large organization, I found myself more and more involved in meetings, not only scientific, which I didn't mind, but also administrative and bureaucratic almost. A lot of papers, office memos. I was spending a great deal of my time at my desk rather than in my laboratory, and I was too young to play that role. I wanted to do something else.

Hughes: How did you approach Swanson with the fact that you were leaving? Or, when you broached it to him, were you looking for some accommodation?

Crea: Well, I expressed my unhappiness and dissatisfaction with my role in different ways, I guess. I waited until I had enough people in my department to be sure that I could leave without disruption. After I hired some senior people to work with me on the chemistry, I felt that with me leaving, Genentech could have gone on its own as before, getting all the DNA they needed. It was at that time that I decided to prepare myself for an exit. Ultimately, I went to Bob's office and I had a very open discussion with Bob, but I had already crossed the bridge.

Hughes: You knew you were going?

Crea: Yes, I told him that there was no second-guessing; I was going to leave. I was going to stay there until everything was ready for transition, but eventually I would leave shortly after. Bob's reaction was of disappointment, but ultimately he looked at me and he said, "I knew that you were going to do something like that." We shook hands and that was inevitable. I mean I'm sure Bob understood my desire to go out and be free to pursue other interests. I promised I wasn't going to hire anybody from the company, and I promised I was going to be available for the transition. Soon after, we agreed that I was going to leave and pass the responsibility to the senior person I hired, and that was the end.

Hughes: Did you ever have any regrets?

Crea: No, no regrets. Well, not from a career standpoint. From time to time I thought that financially I could have been a lot better by staying with the company, but again probably the price would have been too high. I didn't do too badly by leaving either.

Hughes: What were and are the restrictions placed on scientists who leave? How is the intellectual property that you carry in your head controlled? Can it be?

Crea: There's no way you can stop people from using their brain, obviously, and every employer in the world knows that. But in my case, perhaps because the way things had evolved, it wasn't surprising that I decided to go out and start my own company. It wasn't painful to Genentech in the extent that the DNA synthesis support was still there.

Nobody, including myself, had any idea what else was out there to be discovered with my set of skills in DNA chemistry. If I had taken with me some new ideas developed during my employment with the Company, then in that respect I would have had some procedural obligation to Genentech. I was the very first senior person who left Genentech by his own will, and that probably was a first. It was a surprise to Bob, but Bob must have been very busy growing the company too.

Hughes: 1981-82 was a very busy period?

Crea: It was October 1981. So the company was growing very rapidly, and of course Bob had so many challenges and goals in his mind that my leaving probably wasn't a big deal. He wrote a memo to the employees about me leaving. The major disappointment was to leave my team, which I had built in two years. But it was the beginning of a new, exciting experience.

Hughes: Did you keep in touch with your team to some extent after you left?

Crea: Well, physically, the company that I started, Creative Biomolecules, was in the Bay Area. It was not far away from Genentech. We initially started in Brisbane by renting a couple of laboratories and a couple offices from another company. We were in the South San Francisco area, so it wasn't difficult to stumble into old colleagues. I remember I still kept very good friendly relationships with some of the senior people, like Axel Ullrich, Peter Seeburg.

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Crea: There are new people, there are new challenges. That's the incredible environment in which we live. We leave the old, and we are now getting immersed in the new and move on. But my colleagues and some of my coworkers and I still spend some time together. [tape interruption] Some of my early Genentech coworkers and I often go together for lunch, remembering the good old times. [Laughter] In my years of being an entrepreneur, I had the opportunity to meet a number of my former colleagues as well. The relationship has always been good, but never based on working relationship, and no more scientific collaborations. It was a clear cut between Genentech and my new organization.

Hughes: Was that a deliberate break on Genentech's part?

Crea: This is just a guess in my mind. Yes, I believe that Genentech wasn't interested in working with a former scientist who left to start his own company. Again, it was very early. I anticipated what happened later, two, three years later when there was a very large number of scientists who left to pursue their own career as entrepreneurs. But being the first to do it, that was probably perceived as a dangerous trend. Probably the organization at Genentech didn't want to encourage other people to leave and start their own company. In that respect I don't know for sure, but I believe that it was on purpose not to collaborate with my new company.

Hughes: I see, and yet Genentech may hold the record for spawning more CEOs and other top people of biotech companies than any other single company. But of course that was yet to come. You were the first of the wave.

Crea: Yes, and I'm not sure that it was ever a policy that Genentech encouraged internally. Every time a key person leaves, it takes something out. So I believe that with Genentech growing and becoming a pharmaceutical company and shifting its focus from the research to development—clinical development—and business, it was easier to let some bright scientist go out and try his own adventure in biotech. But early on, when the company was heavily relying on the intellectual power of its scientists, it would have been a disaster to let a large number of people go. So I'm sure that I was perceived as a

rebel, maybe a little mad Italian, to leave the big family, the big cocoon, to go solo on his own.

Hughes: Was it ever intimidating? You were leaving a fairly sure thing to go into something whose future was unclear at best.

Crea: No, when I left I was thirty-three years old. So I was still very young to experience and go through mistakes and learn out of your mistakes. I was lucky enough to start my entrepreneurial career when I had some financial latitude from being involved with Genentech early on. The courage comes from being young and being self-confident. I felt that I wouldn't fail because I had too much of an important role early on at Genentech. There were hundreds of new companies being formed which eventually would try to reproduce things that Genentech had pioneered. And also, I believed I could eventually help the industry to expedite that growth.

So I was confident that DNA service, which was my first business focus, would generate a sufficient amount of business to support the new company. But obviously, I wasn't thinking of doing the same thing I was doing at Genentech. Soon the business plan that we put together for my new company, Creative Biomolecules, included the protein engineering aspect, and the mixing and matching with DNA, which is called mutagenesis, in a very precise and sophisticated fashion.

I started developing my own intellectual property. I filed for a number of patents, and I proposed a number of interesting ideas, which ultimately helped people to design different molecules and different proteins, and now we study the function/structure in a more sophisticated fashion. By doing that, I had the opportunity to be involved not only in molecular biology but also in protein biochemistry, immunology, cardiovascular, et cetera

It was a beautiful learning experience by just doing it, and doing it with some original approaches. So, no regrets. Great experiences and a great learning course. Every time I did, I learned something different. Genentech remained this incredible scientific experience and the beginning of my scientific and managerial career; I was at the right place, with the right skills, with the right people, and I was capable of being part of an extremely exciting story. [Laughs]

Hughes: Let me ask you one last question. Of which contribution thus far are you most proud?

Crea: Well, if I had just a single contribution in my mind, I would consider myself old intellectually. I'm always capable of getting excited about the next idea, or the idea I'm pursuing right now. I never thought about the biggest contribution. I think, honestly, that everything I've done in my career has had some degree of creativity and originality. I think this a trend that has characterized my ventures in biotech and maybe even outside biotech.

I enjoy technology and whenever there is a challenge, and I feel I have the tools to participate in that challenge. I really get a kick out of it, and I was fortunate I was capable of making some important contributions. The value of those contributions very often is related to the timing in which the contribution happens, and the context in which it

happens, and the outside support that one might have to develop the positive outcome of those contributions.

I have spent twenty-five years now in biotech, and looking back, some things I've done have been important, some less important. The things I'm still doing today are going to be even more important. [laughter]

Hughes: Good note to end on.

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