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

Conducting Research in Academia, Directing Research at Genentech

With an Introduction by
Susan K. McConnell

Richard Scheller, Ph.D.

Interviews Conducted by
Sally Smith Hughes, Ph.D.
in 2001 and 2002

Introductory Materials

Legal Information

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.

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

> Richard Scheller, Conducting Research in Academia, Directing Research at Genentech, an oral history conducted in 2001 and 2002 by Sally Hughes for the Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2002.

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. 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 generous pledge to support documentation of the biotechnology industry.

Thanks to these generous gifts, 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] The three criticisms leveled at oral history also apply in many cases to other types of documentary sources. 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/.

Sally Smith Hughes, Ph.D.
Historian of Science

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

October 2002

Oral Histories On Biotechnology

Program in the History of the Biological Sciences and Biotechnology

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

David V. Goeddel, Ph.D., *"Scientist at Genentech, CEO at Tularik,"* 2002

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, Inc.,"* 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

"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

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

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

Oral histories in process:

Brook Byers

Stanley N. Cohen

Chiron Corporation

Roberto Crea

Herbert Heyneker

Irving Johnson

Arthur Levinson

G. Kirk Raab

William J. Rutter, Volume II

Richard Scheller

Axel Ullrich

Keith R. Yamamoto

Introduction

by Susan K. McConnell[1]

Susan McConnell and Richard Scheller are married.

"Whatever happened to the little boy with the chemistry set and the microscope?" Richard asked me after spending a long day talking with lawyers and journalists--a day in the life of the Director of Research at Genentech, but for Richard, a day that also represented a diametrical shift from his past life as professor at Stanford University.

Richard Scheller grew up in the suburbs of Milwaukee, Wisconsin, where he dreamed of becoming a biochemist. To Richard's mother Marion, he was her "little scientist," and indeed she and his father Dick bought him those chemistry sets and microscopes which occupied much of Richard's time when he was little. To my knowledge he never blew anything up, but his early experiments did result in many loud bangs at odd hours. The chemistry experiments (at least the ones using formal kits) were set aside during Richard's teenage years, which were spent in what was for the late 1960s a pretty typical set of rebellious behaviors, including membership in a rock band (I can personally attest that Richard cannot carry a tune, so one must hope that the volume of the music made up for what I assume were certain melodic insufficiencies) and the care and feeding of a very large snake that consumed mice. Fortunately for her sanity, Richard's mother was unaware that the process of warming up frozen animal parts involved the pots and pans she used for cooking dinners. Richard's teenage years were characterized by what one might call a benign neglect of scholarly pursuits, accompanied by the growth of quite prodigious amounts of hair. Nevertheless, by the time college rolled around, Richard refocused on his scientific aspirations, entered the University of Wisconsin, buckled down to his studies, and got serious about modern science.

I relate these stories because I think that the spirits of unconventionality and exploration have suffused Richard's work as a scientist from the earliest stages. Richard loves *being* on the cutting edge. Better still, Richard loves *being* the cutting edge. The most well known story about Richard is that as a graduate student at Caltech, he worked with Genentech founders Boyer, Riggs and Itakura, synthesizing the DNA encoding somatostatin and linkers. At the time, Genentech was more an idea than a reality; there was no building to house the company and no cash to pay some kid to synthesize DNA, so Richard was offered stock in exchange for a summer's worth of work. I personally think that he would have done the work for free--it was completely different from the way in which any other graduate student was spending the summer--but the outcome a couple of years later was a photo of a 26-year-old-graduate student on the front page of the *Los Angeles Times,* hair past his shoulders, grinning because the stock he earned was now worth more than a million bucks. This was long before the days of dot.com millionaires, and of course the success and longevity of Genentech as a company has far surpassed these upstart companies, but it is amusing to think of Richard as a forerunner of the brash kids who turned ideas into new enterprises in the '90s.

Richard's success as an academic scientist was framed on his instinct for a good problem and his nerve for taking big risks. Richard's postdoctoral work with Richard Axel and Eric Kandel at Columbia represented a first

breakthrough. With these two advisors, Scheller worked at the forefront of molecular neuroscience, identifying genes that were involved in controlling behavior in the sea slug *Aplysia californica.* In this project, Richard served as a conduit and catalyst between two extraordinary intellects, representing two fields (molecular biology and neuroscience) that were struggling to find a common language. Richard claims to have taught Kandel about DNA and to have taught Axel that *Aplysia* is not a fish. These studies uncovered the first gene known to control a complex behavior (egg laying) and earned Richard a faculty position at Stanford University. A less adventuresome or ambitious scientist would have been content to continue to plug away in this system, cloning neuropeptide genes and exploring the cell biology of egg laying. However, at the time that I first met Richard, he was already gearing up for the major effort that would earn him world-wide recognition. With characteristic ambition, Richard wanted to understand the molecular underpinnings of learning and memory. He realized, though, that if learning involves long-lasting changes in synaptic transmission, then a deep appreciation of the mechanisms underlying these changes could be achieved only if one understood the basic molecular biology of the synapse. He set out to use biochemical methods to purify, sequence, and clone every protein component of the synaptic vesicle, and by God, he pretty much did just that! Those studies and the ones that followed are now viewed as classics, not only in the field of neuroscience but because they laid the groundwork for understanding how membranes are trafficked to specific compartments in all cells.

I believe that Richard's decision to leave academia and join (or, actually, re-join) Genentech was practically inevitable and reflects his appetite for big challenges and his interest in different cultures. Richard is an adventuresome traveler who immerses himself in the place he is visiting. He'll try just about any local food (much to the distress of his digestive system) and loves to talk with local people and fellow travelers. On our trips together, I may quit the campfire or the bar in the late evening, but Richard will stay and talk until the last person disappears. The next day I'll hear all about local politics, the bartender's children, and whatever gossip or complaints or teasing transpired. In many ways I view Richard's decision to head Research at Genentech as one of these adventures in immersion. And immerse himself in Genentech he has--from the start, Richard has talked about the company as "we" and expresses great pride in the company's traditions, policies, and successes. He is particularly proud of Genentech's ability to bring new products to market, and (in paraphrasing a biotech analyst) Richard likes to boast, "We make money the old-fashioned way--we sell stuff."

So while it is true that the daily life of Marion Scheller's "little scientist" is now quite different than when he was at Stanford, the theme of adventure and change is a constant. For Richard, Genentech is a great adventure indeed, in learning about business and realms of science into which he had never before delved, about managing people and making decisions that affect human health and the lives of thousands of employees, and most importantly about translating discoveries in basic science into products that will improve the human condition.

Susan K. McConnell, Ph.D.
Professor of Biological Sciences
Stanford University

South San Francisco, California

December 17, 2002

Interview History

Richard Scheller was interviewed for this oral history series on biotechnology because of his early and current associations with Genentech. At the time of the first interview, Dr. Scheller was six months into his appointment as senior vice president of research at Genentech, to which with some fanfare he took office in January 2001. His thoughts at the outset of a new career should be of interest, particularly his observations on the similarities and differences between the interconnected worlds of academic and industrial research.

As the reader will learn, Scheller's first brush with the company was as a Caltech graduate student. Because of his experience in DNA synthesis which he had used in a project on the lac operator, he was asked to try his hand at synthesizing DNA for the Genentech-sponsored project on somatostatin. Scheller's attempt did not succeed, and he quickly dropped out of the project. But the stock that he received in partial payment and nonchalantly socked away was to escalate in value a few years later at Genentech's spectacular initial public offering on Wall Street, turning him into a temporary millionaire.

A good portion of the oral history has ostensibly nothing to do with Genentech but rather with Scheller's remarkable career in neurobiology, first at Columbia and then for almost two decades at Stanford. His work on neural transmitters in the model organism *Aplysia,* the sea slug, is better told in his own words. From 1994 until his departure for Genentech, Scheller was a Howard Hughes Medical Institute Investigator, a position denoting his high standing in the competitive world of basic biomedical science. [1] Readers wishing more information on Scheller's basic science contributions should refer to an interview conducted in 1989 in the possession of the Hagley Museum and Library, Wilmington, Delaware.

In a deeper sense, Scheller's achievements in basic science and the associations he made with his colleagues have everything to do with Genentech and his appointment to one of its most significant positions. This is the justification, if any is needed, for including discussion of Scheller's non-Genentech career. It was Scheller's reputation as a basic scientist which Art Levinson cited in a press release as a main rationale for his appointment. Since Genentech does not have a program on neurobiology, one can deduce that it was not the specifics of Scheller's scientific research that made him attractive to Genentech. In the oral history, Scheller himself verifies that it was his general reputation as a basic scientist that Genentech wished to enroll and which also gave him the moral authority to make decisions affecting scientists who had been at work in the biotechnology industry far longer than he had.

Oral History Process

Three interviews were conducted in the conference room adjoining Scheller's office in Bldg. 12, Genentech's new research facility. At the first interview, he emerged somewhat bleary-eyed from a five- hour meeting of Genentech's executive committee. He nonetheless settled into the interview, enthused by memories of his early exposure to

science. He seemed to be fully engaged in this and subsequent interviews. With the exception of a few pages, he did not review the transcripts.

The reader will note that the discussion veers from strict chronological order. These interviews, as well as others conducted at this time, were affected by the litigation Genentech was currently engaged in with City of Hope. As a result, Genentech asked that discussion of its earliest projects--somatostatin, insulin, and growth hormone--be deferred until the conclusion of the case. As a result, Scheller's description of his work on somatostatin, constituting his first contact with Genentech, occurs out of order in the third section. Also according to agreement with Genentech regarding the oral histories it supported, 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 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.

Sally Smith Hughes, Ph.D.
Historian of Science

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

November 2002

I Family Background and Education

[Interview 1: August 16, 2001]## [1] ##This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

Childhood Wish to Become a Scientist

Hughes

Please tell me about your family and early education.

Scheller

Oh my goodness. I was born and raised in Milwaukee, Wisconsin, in the Midwest. It was a wonderful place to grow up. My father was a social worker and a hospital administrator. My mother was a housewife for many years of our childhood and then went back and received her bachelor's and master's degrees in art.

I always wanted to be a scientist. As a child I had chemistry sets and microscopes, and I had a laboratory in the basement of our house. I would spend hours there doing experiments. My mother used to call me her little scientist.

Hughes

What triggered your interest?

Scheller

I have absolutely no idea. I was just fascinated with the physical world around me and wanted to understand it in logical terms. I can't really recall any specific trigger. My father and mother are not scientists, my grandparents are not scientists, but somehow I believe being a scientist is something innate in my DNA because it goes so far back.

Hughes

Did that interest continue all the way through school?

Scheller

Sure. I would say I was not an outstanding high school student. I was good in chemistry but not particularly focused even though I knew I wanted to be a scientist. I actually even knew in high school that I wanted to be a biochemist.

Undergraduate, University of Wisconsin, Madison, 1971-1975

Biochemistry Major

Scheller

I knew that the University of Wisconsin in Madison was a very strong school for biochemistry because of their history in agricultural chemistry which evolved over the years into biochemistry. And I knew that with an average high school background, in state, I would be admitted to the University of Wisconsin, and that I would catch up then.

Hughes

Isn't there a separate institute of biochemistry at Wisconsin?

Scheller

There's the Enzyme Institute, which is largely a school for enzymatic studies, which is mostly biochemistry. But remember, the University of Wisconsin is a place where there are 50,000 students. There's a genetics department, a microbiology department, a biochemistry department, enzymology, zoology, molecular biology, cell biology, and it goes on and on. It's a huge place.

Hughes

And you were in the department of biochemistry?

Scheller

I was, which interestingly is in the school of agriculture because of the history there: The discovery of vitamin D and, as I mentioned, the biochemistry department formally being called agricultural chemistry.

The funniest thing I remember about that is in my freshman year being recruited to be in a fraternity in the agriculture school, which is mostly comprised of people that were training to be dairy farmers. [laughter] Most of the people did not grow up in the city. It was very funny when I was invited to their fraternity house for a recruiting dinner, and I told them that I wanted to be a biochemist. Clearly, this did not fit in with this group of people in the ag school.

Hughes

Did you have friends who were interested in non-agricultural biochemistry?

Scheller

As friends, and certainly as colleagues in my classes, and so on, sure. I became at that time a very, very serious student where I studied day and night for four years and learned biochemistry.

Hughes

What attracted you to biochemistry?

Scheller

As I said, I honestly don't know. I wanted to be a scientist, a chemist, and a biochemist, even in high school. I think what attracted me was that as a child I liked microscopes; I liked the study of biology; I liked living things, but I also really enjoyed chemistry. I think that at a very early age, twelve years old, thirteen years old, it emerged as an amalgamation of my "scientific" interest. That's really the earliest that I can trace things.

Undergraduate Research

Hughes

Did you do any research as an undergraduate?

Scheller

Yes, I worked in two laboratories. As my earliest research, I worked in an oncology group, studying the metabolism of the amino acid tryptophane in patients with bladder cancer. I then studied in the biochemistry department in an x-ray crystallography group, which resulted in what eventually turned out to be my third publication, because it came out after I left Wisconsin--a publication in collaboration with some of the then graduate students at the University of Wisconsin. [2] See #3 in Scheller's bibliography in an appendix to this oral history.

Hughes

Was it unusual for an undergraduate to be publishing with graduate students?

Scheller

I think it was a little bit unusual. It's not unheard of.

Hughes

Were you actually doing crystallography?

Scheller

I was doing crystallography. I was also purifying the molecules and growing the crystals, doing molecular modeling studies.

Hughes

How were you learning these techniques?

Scheller

By working with the graduate students and the postdocs that were there. I became good friends with them, and even actually see some of them today, which now--I don't even want to think about it--is thirty years later. They're professors at various universities and they shake their head and think, "This is that undergraduate that worked with us."

Hughes

Did you have any particular relationship with any of the faculty members?

Scheller

I knew a variety of the faculty members. I'm not sure that I was particularly close to any individuals.

Hughes

So you didn't have a mentor at that stage?

Scheller

Not really. I think there are a lot of very dedicated teachers at the University of Wisconsin. I thought that the classroom lecturing was generally outstanding. There were tremendous opportunities, even at a large state school, to do individual research and an honors undergraduate thesis. I have had a little more experience with different universities now and can look back and say the University of Wisconsin is an absolutely terrific, first-rate institution. I owe a lot to them for the education that I received there. Even though there are 50,000 students there, they're taught well.

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Graduate Student, California Institute of Technology, 1975-1980

Richard Dickerson, Arthur Riggs, and Research on lac Repressor Protein

Hughes

How much of this education were you destined to use when you moved to graduate school?

Scheller

That's an interesting question, because I think my interest in x-ray crystallography shaped the choice of graduate school; it shaped the laboratory that I joined; and that shaped the whole rest of my life, of course. I was interested in atomic structures and biological molecules and the way the structures determine the function of the molecules. I had read a book by a professor at Caltech; Richard Dickerson is his name. I don't know if his name has come up in your other discussions, but it should.

Hughes

It hasn't, but I've certainly seen it in the material I have on you.

Scheller

I decided that I wanted to work with him. I think I also heard a seminar that he presented at the University of Wisconsin, so I applied to graduate school at Caltech specifically to work in his laboratory. Again, that was really based on my undergraduate research experience and the interest that I had developed in x-ray determination of biological structures.

Hughes

I don't imagine there were too many undergraduates who could present such a background.

Scheller

Probably not too many.

Hughes

Was Dickerson doing x-ray crystallography himself?

Scheller

Oh yes. He's a famous x-ray crystallographer. In about two months I'm going to a symposium in Los Angeles for his seventieth birthday. It will be held at the Getty Museum. It should be a lot of fun. I'm an invited speaker at this symposium, so it's a chance for me to show that I've made something of myself.

Hughes

Tell me about Dickerson as a personality and what it was like being in his laboratory.

Scheller

The reason I became very interested is that we had an idea that we would solve the atomic structure of the lac repressor protein bound to the operator DNA. This is a classic system in bacteria for regulating the expression of the gene. This is actually the system that [Francois] Jacob and [Jacques] Monod worked on, which they won the Nobel Prize for. The specific question that we were interested in is how the repressor protein binds the DNA in a specific place. The *E. coli* chromosome is 4 x 10^6 nucleotides of DNA, and this protein was able to pickout twenty-one nucleotides of that 4 x 10^6 and very specifically bind to that site and shut off expression of the gene. We wanted to understand that recognition process at an atomic level.

Hughes

The fact that the gene was shut off had already been worked out by Jacob and Monod?

Scheller

And others.

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Hughes

And others.

Scheller

When the appropriate signal was presented in the environment, a molecule would bind to the repressor so that it would fall off the DNA, and that would then allow expression of the set of genes. It was the way that the bacteria sensed the nutrients in the environment and regulated their gene expression accordingly, so that they could metabolize the nutrients appropriately.

Hughes

This was a pretty hot area of science, was it not, at that time?

Scheller

It was really a very interesting area, sure.

Hughes

A lot of different laboratories were competing, were they not?

Scheller

Anything that's interesting, a lot of laboratories are usually competing.

Here's where the story gets interesting in terms of the specific connection to Genentech. At the time we needed to isolate the protein and the DNA. The protein one could isolate; the person, Art Riggs, who was an expert in isolating this protein worked at the City of Hope [Medical Center], just down the freeway. I forget which [exit] number it is by now, but it's down the freeway from Caltech. Riggs had a collaboration with Dickerson at Caltech to isolate the protein. The problem then was that we needed the DNA, and DNA at the time was extremely difficult to come by, especially large amounts of a very specific sequence. So Dickerson and Riggs thought that maybe instead of isolating the DNA from a natural source, that perhaps one could synthesize the DNA chemically in a test tube, bind it to the protein, crystallize that complex, and then solve the atomic structure.

DNA Synthesis

Hughes

Gobind Khorana is a name that I associate with DNA synthesis. Are we talking about the mid-'70s? Had Khorana done his work by that time?

Scheller

Khorana was working with a hundred people for years to synthesize the tRNA [transfer RNA] gene. Even to synthesize the twenty-one base-pair DNA for the lac operon by Khorana's method would have been extremely difficult and time consuming; and to make a strand of DNA twenty-one [base pairs] long would be very hard and would have probably taken years. When you're done you wouldn't get very much, etcetera. A Japanese chemist working in Canada with a former student of Khorana's had invented a different way of synthesizing DNA; his name was Keiichi Itakura.

Hughes

Are you going to tell me how his way was different?

Scheller

Yes. What Keiichi did was to put a protecting group, we call it, to modify the DNA by putting a chemical entity on the phosphate of the DNA backbone so that the DNA was no longer negatively charged. He put a parachlorophenol, was the name of the group, on the phosphate backbone of the DNA so that it was no longer negatively charged. That meant that instead of

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having to work in solution, in water, the chemistry could be done in organic solvents. Organic chemistry was a highly developed field even then, with much better-understood properties of the chemical components. The DNA was much easier to synthesize in organic solvents than water. Then when you were done with the synthesis, you removed all the protecting groups and you were left with DNA.

Hughes

So Khorana had been working in a water medium?

Scheller

Yes.

Hughes

And that had slowed him down, made it more difficult?

Scheller

Yes. Riggs and Dickerson knew about the work of Itakura, and they brought Itakura to Caltech. And Itakura 99 percent-- (I'll say "we" because I arrived at Caltech about the same time as Itakura, within a couple of weeks of each other.) We set up--although I knew nothing about it; he did--a DNA synthesis lab at Caltech. Our goal was to synthesize the lac operon DNA. Riggs and the scientists that he was working with at the City of Hope and at Caltech would purify the repressor protein, and then we would mix them together to solve the crystal structure. We never did that. [laughs]

Hughes

You mean you never solved the crystal structure?

Scheller

Right. But a few years ago [it was solved] by someone else. It took twenty years in between to actually get it done. That was the idea at the time, and that's what brought Dickerson, Riggs, Itakura, and me together. In fact, Dickerson was the nucleus of this event.

Dickerson's Laboratory

Hughes

Tell me about him and how he got to this point in his research interest.

Scheller

As I said, he's a famous x-ray crystallographer who worked at the MRC [Medical Research Council] Laboratories with the people that invented protein crystallography. Max Perutz won the Nobel Prize. Dickerson was a renowned chemist and crystallographer and professor at Caltech. He's a very good teacher. He wrote textbooks. I remember one of the things that he asked me to do one weekend was to solve all of the problems in the chemistry textbook that he had written so that he could compare my answers to his answers to make sure that they were right. He paid me $100 or something for that, which at the time was a huge amount of money.

Hughes

And they did match?

Scheller

They matched for the most part, I think; I don't really remember the details, but certainly they mostly matched. I had to solve these several hundred chemistry problems though. I say now I had to solve them because it sounds like quite a chore, but back then for $100 I was very enthused to solve them all. [laughter]

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We worked in the laboratories that were occupied by Linus Pauling when he was at Caltech. Some of the protein models that were in some of the laboratories in the halls that I walked up and down were actually made by Pauling and his workers. It was really a very historic place.

Hughes

How many of you were there, aside from this group working on the lac repressor?

Scheller

Other technicians and graduate students and postdocs.

Hughes

With different projects?

Scheller

Yes. Some of whom were working on this project with us. Some people were working on the protein component as I was working on the DNA component, and others were working on other projects.

Hughes

Why were you working on the DNA component?

Scheller

I'm not sure there was a particular reason. I think because Itakura came to Caltech at about the same time and needed help setting up the lab; it seemed like a natural thing. I know that [I was] Keiichi Itakura's first graduate student. We became very good friends. We've drifted apart over the years, but at the time he was really my mentor. Dickerson was so famous that he spent more time in the office, while we spent time in the labs, similar to what I've been doing for the last ten or twenty years.

Hughes

Was DNA in itself then a real focus of biochemical attention? Because it hadn't been early on in biochemistry.

Scheller

Right.

Collaborating with Herbert Boyer to Clone lac Operator DNA

Scheller

I think the next thing that happened is very interesting and important because it's the connection that brought Herb Boyer into the picture. It was the thought that the DNA that Itakura made was good DNA, but it still wasn't quite enough. So we wondered--mostly Riggs, and Itakura, and Dickerson--we wondered whether we could clone the DNA. There was a very easy way to know if you've cloned the lac operator DNA because if you put the binding site of the protein into the bacteria, you would suck the protein off of the bacterial chromosome because it would bind the plasmid that contains the synthetic DNA, and that plasmid was present in maybe ten or twenty copies inside the bacteria. So you would suck it off the chromosome because it would bind the plasmid DNA, and that would then turn on the gene. You could see that by the bacteria colony turning a certain color if you gave it the right substrate. So Riggs and Itakura gave the DNA to Boyer who had just invented the cloning method. Boyer's group--Herb Heyneker I think in particular; I don't remember exactly who--put Itakura's synthetic DNA into the bacteria.

The interesting thing about Itakura's synthetic DNA is it was twenty-one base pairs and it had flushed ends. I wanted to put it into the EcoR1 restriction enzyme site. Boyer had a piece of synthetic DNA that was eight nucleotides long that contained the EcoR1 restriction enzyme site which he was using to study the properties of the restriction enzyme.

Hughes

Had he made the DNA?

Scheller

That was probably made the Khorana way. I'm not sure who made it.

Hughes

Heyneker knew how to synthesize DNA?

Scheller

No, Heyneker was a molecular biologist.

Hughes

Well then, who was doing the synthesis?

Scheller

Boyer collaborated with someone.

That was an eight base-pair piece of DNA which was symmetric, meaning that it hybridized to itself. Its sequences were the same reading forward and backward, so you only had to make eight nucleotides. The lac operon was twenty-one nucleotides. It was not symmetric, so that was forty-two nucleotides that you had to make. I would say to make forty-two nucleotides versus eight was one thousand times harder.

What Heyneker did was to ligate the eight base-pair EcoR1 sites onto Itakura's twenty-one base-pair site, then to cut with the restriction enzyme, and then to place this piece of synthetic DNA into the plasmid, and the plasmid into bacteria. That actually was the first cloning of DNA made in a test tube. That was done before Khorana.

Hughes

Oh really?

Scheller

Absolutely. No doubt. It's in the historical record of the publications; it was published first.

Hughes

Do you remember the year?

Scheller

It would be referenced in the *Science* paper on linkers. [3] Scheller bibliography, reference #1. [Pause while looking for the reference.] Then that gave rise to the idea that it would be useful to have synthetic restriction enzyme recognition sites useful for cloning.

##

Scheller

I then synthesized the Hind III, BamH1, and EcoR1 restriction enzyme sites and showed they were cut by the enzymes and so on. That's the 1977 paper in *Science,* which is hard to believe, because now if you want a ten-base pair of DNA you just e-mail your request to your synthesis group, and if you don't have it by the next day you're wondering what they're doing and why it's taking so long.

Perhaps more importantly for historical purposes, this is where Riggs, Itakura, and Boyer got together. It only takes one more person to make Genentech.

Scheller's DNA Linkers

Hughes

Getting back to that first paper: It was more, I thought, than the fact that you made linkers with restriction sites. It was also the fact that they had sticky ends, is that not true?

Scheller

Sure, well that's why they were put on in the first place; that was the whole point.

Hughes

What was new about what you did other than the fact that there were restriction sites?

Scheller

People had cloned pieces of DNA with sticky ends into restriction enzyme sites. The problem was that a lot of times, probably most times as a matter of fact, the piece of DNA that you would want to clone didn't have sticky ends. You wanted to put the sticky ends onto your DNA so that you could clone it. That's what this [method] allowed one to do, and has in fact been used by [Peter] Seeburg, and [Axel] Ullrich, to clone the cDNA [complementary DNA] for insulin, clone the cDNA for growth hormone, and so on. I remember I sent out these pieces of DNA to scientists all over the country, all over the world, to be able to use them for their cloning experiments because there was nowhere else you could get them.

Hughes

Do you have a record of the laboratories that you sent linkers to?

Scheller

No.

Hughes

Wouldn't that be a rough profile of laboratories that were early into recombinant DNA?

Scheller

It would be some measure, sure. I know I sent them to [Mark] Ptashne and [Walter] Gilbert at Harvard. I know I sent them to UCSF.

Hughes

Because you had originated this way of linking.

Scheller

Sure. You write a paper on just [their] synthesis--this is trivial by today's standards.

Hughes

It shows you how far the field has advanced. But there were other methods for linking pieces of DNA, even at that time, right?

Scheller

They were less efficient; they were harder to do, and they weren't as convenient. This method was also convenient because when you put the DNA in with a restriction enzyme site, and then you propagate it through the bacteria, and then you isolate the plasmid, you can also cut the DNA out again. If you put it in other ways it's much harder to retrieve.

Hughes

So it became the preferred method?

Scheller

A preferred method, sure.

Hughes

I'm thinking of the Stanford group around Paul Berg which was recombining DNA in different ways. There was the tailing method, for example.

Scheller

The problem with the tailing method is it didn't allow you to cut the DNA back out afterwards.

No Memory of the Introduction of Recombinant DNA Technology

Hughes

What about your early memories of the Cohen and Boyer work on recombinant DNA? Do you remember when you first began to hear about it, and how?

Scheller

Not really. When I moved to graduate school [1975] it pretty much had become quite routinely used, although the methods were very primitive compared to what we do now. The Cohen-Boyer work, when was that done?

Hughes

Three papers were published in 1973 and '74.

Scheller

I was an undergraduate then, and that kind of thing didn't really enter my world until graduate school. In graduate school it was something that was being pretty commonly done. I just don't remember; I was not a practicing scientist; I was a classroom scientist when the work was done. And I was studying x-ray crystallography, not molecular biology, so it didn't really rock my world. [laughs]

Hughes

Nonetheless, when you arrived at Caltech in 1975, this technique was at most two years old, and yet it was an accepted routine for people doing biochemistry or molecular biology? Nobody thought much about it? It was just another technique?

Scheller

Yes. As I say, it was very primitive compared to the way we practice it now. Just another technique. Every lab at Caltech that wanted to used recombinant DNA, and that was many, many, many, many laboratories.

Dickerson, Riggs, and Keiichi Itakura

Hughes

You haven't told me very much about personalities. Start with Dickerson if you don't mind. What was he like? How would you characterize him?

Scheller

Dickerson was a very big-picture guy, a little bit aloof I would say.

Hughes

British?

Scheller

No.

Hughes

You said MRC--

Scheller

He was a postdoctoral student there. I'm not sure where he was a graduate student. He really was not as interested in the details of the experiments as others. He's a very good undergraduate teacher and lecturer in chemistry. Many of the undergraduate students at Caltech took freshman chemistry from Dickerson. [He was] interested in organizing big science projects--although they wouldn't be big by today's standards--like trying to do this lac operon repressor crystal structure, which involved Riggs and bringing Itakura from Canada, and so on.

Hughes

He facilitated that?

Scheller

Yes.

Hughes

And he planned the general orientation of the research?

Scheller

Yes. I think that he and Art Riggs planned the research. Art Riggs was much more technically oriented, had more experience with this specific protein biochemistry, not with the x-ray crystallography. I think that Art Riggs was conservative scientifically and very precise and rigorous.

Hughes

Meaning that Dickerson wasn't?

Scheller

Well, Dickerson didn't even deal with things at that level.

The person that we haven't talked about is Keiichi Itakura. I worked side by side with Keiichi in the laboratory. He's really the one that taught me how to synthesize DNA, and he's the one I worked closest with. I was twenty-two or something like that. I was very, very impressionable in all ways.

Hughes

Tell me about Itakura.

Scheller

He was a very fun guy. He didn't speak very good English. I probably communicated with him more than anyone else just because we were standing or sitting next to each other all day, every day. He had a very lovely wife and a nice family. He worked extremely hard. I think that he had lived in Canada for a number of years but was still very Japanese in a number of his mannerisms and ways and, as I said, not particularly easy to communicate with. But he was a friend of mine.

I remember that I didn't have a car at the time so I borrowed his car one evening to go out on a date. I think he was quite nervous in loaning it to me, making sure that I brought it back. He lived close enough to me that I could just return it and walk home to my house from his house. It's one of those things you just remember as a funny event.

Applying Recombinant DNA to Gene Expression in Animals

Hughes

Should we skip to the research you did at Caltech?

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Scheller

Since recombinant DNA was becoming very widely used by anyone who wanted to do the technique, I thought that one of the most intriguing problems in all of science was, and still is, how a sequence of DNA is read out and interpreted to give an animal. There was a lot of excitement that we might be able to understand how gene expression is controlled in animals in the same way we understood how lac operon was turned on and off in a bacterium. And if you could understand that in animals, that would really be the key to how differential sets of genes were expressed in different cells and throughout development to give rise to adult organisms.

There were ways, but no real promising ways, to study that before recombinant DNA came along, because the genetics of animals is very tedious, unlike [that of] bacteria. There was no way to get the DNA. You could make DNA from an animal; that was fine. But then you had 3×10^9 nucleotides of DNA in a test tube; what would you do with it? The notion that you could take the DNA of an animal and cut it up into little pieces and use recombinant DNA to clone the DNA to isolate specific sequences of animal DNA then meant that you could study that piece of animal DNA, perhaps figure out how it worked at the same level of understanding as the lac operon. That was a big deal. It was very, very exciting.

Hughes

How would a researcher select the specific segment of DNA that he chose to work on?

Scheller

That was a problem at the time. Sometimes, for instance, you could start with the RNA, and make the RNA into DNA, and then put linkers on the end, and then clone it. If you worked with a blood cell, almost all of the RNA in the blood cell encoded globin (the red part of our blood). So you could get the globin cDNA just by looking at any random clone made from blood cells because most of them would be that sequence. It was primitive kinds of things like that, that you had to use in order to get a specific piece of DNA. Other people studied random pieces of DNA; a piece of DNA from an animal is bound to be important for something.

Hughes

If you had a random sequence of nucleotides, how were you going to link them up with function?

Scheller

People had all sorts of ideas. As a matter of fact, it turns out that it's still a very hotly investigated area of science.

Hughes

You're thinking of the Human Genome Project?

Scheller

Well, I was thinking: Do we know now how sperm and an egg come together and read out the DNA to make an animal? No. We know a lot more than we knew twenty years ago, but it's not as simple as the lac operon. People thought if you had the DNA, for example, that you could look for proteins like the lac repressor that bound to the animal DNA, and say, "Stop! There's a repressor-like protein." People thought if there were ten genes turned on in a particular cell, like a liver cell, all the liver genes might have a particular DNA sequence in front of them that might say, "This means you have a liver gene." The piece of DNA would be a binding site for a protein or a transcription factor that would turn on the DNA in liver. So if you just looked at the DNA from ten liver genes, and they all had nothing in common except this particular region, then that region would then likely be important. There were a lot of those kinds of ideas that we were all sure would work out much more quickly than they did. This is still an issue, as I said, that people are investigating and doubt. But that was an

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extremely exciting time because, as I said, recombinant DNA was being widely utilized to study whatever particular problem you wanted to study.

In '77 there were cDNA libraries being made, so copies of the mRNA [messenger RNA] from different cells were being put into bacteria. Then genome libraries were being made so that the DNA in the nucleus was being cut up into pieces and cloned into bacteria. I know that there were libraries from rabbit, *Drosophila,* sea urchin, mouse. These were the labs of Norman Davidson (*Drosophila*), Tom Maniatis (rabbit) who was then a professor at Caltech, Leroy Hood (mouse), Eric Davidson (sea urchin). These were some of the first whole genome libraries that were made.

Hughes

By what time?

Scheller

Seventy-seven. One could then go into the libraries and find the genes.

Hughes

Were they making these libraries available to anybody that wanted them?

Scheller

Probably; I'm not sure. It wasn't so easy to copy the libraries back then.

Hughes

Why was that?

Scheller

As you propagate them, they change their representation; some clones grow a little better than others. I don't really remember. I presume they were made available for other people.

The Recombinant DNA Controversy

Hughes

The recombinant DNA controversy was going on in the mid to late 1970. How much were you aware of it, and did it shape the way you were doing your science?

Scheller

I was aware of it because Tom Maniatis moved to Caltech specifically because of some issues revolving around this controversy. He moved to Caltech, I believe, in part because some of the controversy in Cambridge, Massachusetts, where he was not able to do all of his work at Harvard. Perhaps that was one of the reasons--you would have to ask him--that he moved to Caltech. At the same time, [Robert] Sinsheimer was the former chairman of the department of biology at Caltech and was actively involved in the controversy.

Hughes

On the other side, right?

Scheller

That's right.

Hughes

What did that mean for scientists working in recombinant DNA?

Scheller

We didn't really take it very seriously. I think that people pretty much believed that of course you wouldn't want to propagate DNA from a very active or dangerous virus, but that the work that we were doing was relatively harmless. We were careful to dispose of materials

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appropriately and to wear gloves, and so on. There was no real concern by most people that anything we were doing was dangerous. I think the largest concern was that there would be some kind of moratorium to keep us from doing our work.

Hughes

And there was.

Scheller

There was--for certain kinds of work: cloning from tumors or cancer cells, cloning of certain kinds of viruses. The moratorium, as a whole, was really quite short. It really didn't affect anybody very much. It was also voluntary, if I remember [correctly]. There was no enforcement really.

Hughes

It was a scientist-imposed moratorium and where was the regulation? There was no governmental regulation.

Scheller

I think that it was voluntary. Some people paid attention and others just totally ignored it. It's not like the police were going to come or anything.

Hughes

Were you aware of the political machinations of that period, or were you just doing your science?

Scheller

I was aware of it and thought it was all absurd.

Hughes

How could you be sure?

Scheller

I can't be sure, but it seemed that we understood the biology better than anyone else in the world since we were the ones that were working with it, inventing it, modifying it, and so on. Our best technical assessment was that it was not dangerous. One can't be sure. Remember, I was twenty-two or three or four, or whatever I was; I was immortal then, of course.

Hughes

Yes, exactly. [laughter] It's not an age where you're looking for reasons not to.

Scheller

That's right. Just do it!

Hughes

The NIH guidelines came into force in 1976. Was there much notice paid in the laboratory?

Scheller

I'm sure we abided by the guidelines, but that basically just meant having a room set up in an appropriate way for the kinds of work that were going on. I worked mostly with sea urchins which are not mammals. They required a fairly low biosecurity level of containment, which was basically a room that had somewhat limited access where you autoclave things when you are done. It really wasn't much of a constraint.

I think it was good that the scientists thought about it; I think it leant a legitimacy to the endeavor. It assured people that scientists were thinking about potential dangers. It did lead to the use of bacterial strains and bacterial virus strains that are weakened compared to those that live in the wild, so that even if they did "escape" from the laboratory they wouldn't survive. I think it was a good thing to do on the same kinds of strains.

Hughes

Were you using them as well?

Scheller

Sure.

Hughes

Were they hard to work with?

Scheller

Not particularly. We could pamper them in the laboratory so that they would be very happy growing there; they wouldn't have to compete with all those tough bacteria that live out in the wild.

Hughes

The picture you paint is: Yes, there was an awareness of the political situation, but all these issues were not having a tremendous impact on what you were doing. You pretty much carried on as you had before the recombinant DNA issue arose, within certain limits.

Scheller

"Tremendous" is an overstatement. It had very, very little effect on us doing the work in the laboratory. Very little effect.

Hughes

Do you remember the controversy having any effect on the problems that you chose?

Scheller

No. We followed the interesting scientific problems. As I said, I think there was some fear that there might be some rules imposed that would get in our way, but there never were.

Hughes

And there never was federal legislation, for many reasons. One of the reasons was that by the late '70s the commercial potential of recombinant DNA was becoming more obvious; recombinant DNA was seen as a technology that might rescue the flagging American economy.

Scheller

I'm not sure that that really played a role. Maybe you know differently; you study this. But I'm not sure it played a tremendous role in influencing safety guidelines. I think that if scientists honestly believed that [recombinant DNA technology] was unsafe, even if it was possible to make a lot of money, they would have imposed guidelines. I think the vast majority of scientists honestly believed that with relatively simple precautions this technology was not dangerous!

Richard Sinsheimer's Concern about Recombinant DNA

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Hughes

Do you have any insight into why Sinsheimer questioned the use of recombinant DNA?

Scheller

I didn't really know him very well. He was chairman of the department [Division of Biology] at Caltech before I arrived. As a graduate student, I really didn't interact with him very much. He was thought of by us as someone on the other side of this debate, but I never really interacted with him so I don't really know.

Hughes

It didn't cause a schism in the department?

Scheller

He moved to Santa Cruz.

Hughes

He became chancellor.

Scheller

I don't remember exactly when, but he left Caltech and became chancellor, and then there was no schism in the department because he wasn't there!

Hughes

But when he was there, there could have been hesitation, or at least more care, about how one used recombinant DNA. If you had a critic who happened to be chairman of the department--

Scheller

But he was not chair at the time. He was formerly chair of the department. I think Lee [Leroy] Hood was chair of the department at the time and was one of the aggressive users of recombinant DNA. Since Sinsheimer was former chair, he was probably entertaining other administrative positions where he wouldn't run a laboratory anymore, and then soon moved to Santa Cruz. I have a memory of him being on the other side of the debate, but nothing really very specific beyond that.

Interacting with Leroy Hood's Laboratory

Hughes

Did you have any specific ties with Lee Hood or his laboratory group?

Scheller

Well, some of his students were in the laboratory next to mine. One of the students in the lab that was next to mine is now on the faculty at Stanford; we were both on the faculty there for the last twenty years before I moved here. I interacted with his students routinely. We shared reagents and ideas and things.

Hughes

Was it a pretty communal place?

Scheller

Absolutely, absolutely. The techniques and reagents were shared. At the time, we also made things like enzymes. They were quite expensive back then, so we had a laboratory that would purify restriction enzymes for us. The technician worked on purifying the enzymes and would make $200,000 worth by the catalogue price in a couple of weeks and would distribute them to the different laboratories. We conserved on money by making them ourselves. There were only a few different restriction enzymes that were known back then. Hood's students also rotated in making radioactive ATP; one person would do that every week and then share it with the whole group.

Hughes

You being one of those students?

Scheller

Sure. We went over to the physics department and used a laboratory specific for radioactivity.

It was a very, very, very communal feeling back then because we really weren't competing with each other. We were using different experimental organisms to ask different questions but using common techniques. So we shared the techniques, and our specific experiments were not in any way competitive with each other. It may have been the perfect kind of atmosphere to collaborate or cooperate, whatever the case may be.

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The Sea Urchin as Experimental Organism

Hughes

You mentioned that you took up research with the sea urchin. I'm assuming the overall goal was to get a better handle on how higher organisms developed, as opposed to *E. coli* ,which you had been working with first.

Scheller

Yes.

Hughes

Were other people working in non-bacterial organisms?

Scheller

Well, sure. People worked in *C. elegans,* and *Drosophila,* and sea urchins, and rice--

Hughes

I meant right in your lab group.

Scheller

Eric Davidson's laboratory group focused on the sea urchin. It is quite common for a laboratory group to focus on a specific experimental organism. We studied the sea urchin because we were particularly interested in early embryonic development, meaning one cell going to two, four, eight blastula-gastrula stages. Of course in a mouse or a human that's very hard to study because in a mouse, for example, you might have six or so embryos that are fertilized at a time. I don't know if you've ever had uni. That's sea urchin gonad; it's a sushi ingredient.

Hughes

I've heard of it.

Scheller

I love uni. If you inject the sea urchin with the appropriate salt solution it will deposit its eggs and it can be millions of eggs. It's the eggs that sperm will fertilize, and they go through development ina relatively synchronous way. It's possible to obtain many hundreds of thousands and millions of embryos from the sea urchin, versus six from a mouse, which would not be very much material to work with. So that was the reason for studying sea urchins.

Scheller's Research on Embryonic Development

Hughes

Tell me what you were interested in.

Scheller

The question was the issue that I raised earlier: How does the linear sequence of the DNA give rise to a complex, three-dimensional, thinking, breathing, adult organism?

Hughes

Nice, narrow question.

Scheller

I believe sea urchins think, not of course the same way we do. In particular our focus was on those very early stages of development.

Hughes

So you were narrowing it down, because that seems to be a tremendously broad question.

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Scheller

Sure. The idea was that we could study the expression and the roles of specific DNA sequences that we isolated through recombinant DNA methods during these early stages of development.

Some of the people in Eric Davidson's lab were particularly interested in DNA sequences that are repeated many times in the genome. Some pieces of DNA are present only one time in the nucleus, and others maybe a hundred times or a thousand times. There was an idea, as I mentioned before, that these repeated sequences might be landmarks in the DNA that are important in determining the expression pattern of the DNA. We isolated these repeated sequences using some tricks and were studying the way they were expressed and the way they were organized. That was part of the work that I did.

Scheller's Research on the Actin Genes

Scheller

I also studied this specific set of genes called the actin genes; [they are genes] for a component of the cytoskeleton. They is a family of these genes, I forget how many, maybe five or ten related genes that turn on and off in specific cells in specific patterns. I believe Eric Davidson's laboratory group at Caltech still studies these actin genes and is still trying to answer the same question that we set out to answer years ago about what controls their expression.

Postdoctoral Fellow in Neuroscience, Columbia, 1981-1982

Reductionism

Hughes

One paper that I looked at while I was waiting for you was a 1983 paper in which you were finding that one gene, the gene encoding egg-laying hormone-- [4] See #14 in Scheller bibliography in appendix.

Scheller

That's when I left Caltech to go to my postdoctoral studies at Columbia. I became interested in trying to understand, at a biochemical or a molecular level, why it is that animals do the things that they do, their behavior. Of course if you're a biochemist you're a reductionist, which means that we should be able to explain all aspects of life--not only how an animal develops--through an understanding of cells and molecules. But we should also be able to understand behavior through an understanding of cells and molecules.

Hughes

And you believe this?

Scheller

Sure, what else is there? It's your brain after all. Your brain is made of cells and molecules.

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Unless you believe in some spirit or life force that tells you what to do, something that a scientist would have trouble with, it's really all we have. So of course I believe that.

Hughes

Do you agree that it's not quite as simple as it was originally pictured to be in the Central Dogma?

Scheller

Nothing is as simple as--I shouldn't say nothing is as simple. Things in science tend to go through phases where you think it will be simple; you find out it's complicated, but then once you understand it, it seems simple again. I'm not sure what stage we're at in life science right now. I think, actually, we're at the complicated stage right now. [laughter]

Eric Kandel

Scheller

The famous scientist at Columbia who won the Nobel Prize last year, Eric Kandel, had been one of the early scientists who thought that if you could understand behavior in terms of the neural circuitry, you could understand the neurons that mediated the behavior, and then you could modify that behavior with experience, and then study the ways cells had changed. You could understand where the memory was which resulted in the change of the behavior. We, as neuroscientists, still believe that's the case. Kandel's training was as a psychiatrist but a very biologically oriented psychiatrist.

One of the things the animal (which was a marine snail, *Aplysia*)that he studied does is to lay eggs in a very stereotypic pattern. All of the animals lay their eggs in the same way: the egg string is excreted from the back. They hold the egg string in their mouth, and they move their head back and forth in a line--it could be a long string of eggs if it was in linear sequence; it could be several meters. They wind it into a coil and deposit it as a sticky mass on the side of the tank, or in the wild maybe on a rock or a leaf or what have you. All of the animals lay eggs that way. They're born knowing how to do it; they don't have to learn how to lay eggs that way. This innate behavior somehow has to be encoded in their DNA, in their nerve cells, and their chemical communication between the nerve cells.

The advantage of studying this animal is not only that they have relatively simple behaviors--the snail doesn't do a whole heck of a lot: it eats and has sex, lays eggs, and that's pretty much it--but that there are only about 20,000 neurons in the animal. Some of the cells are extremely large; they're up to a millimeter in diameter, so you can see a single cell with your naked eye; it's tiny but you can see it. The makes it, of course, easier to do electrophysiological studies or even biochemical studies, because of the large size, relatively small number, and the stereotypic organization of the cells.

Scheller Clones the Gene for Egg-laying Hormone

Scheller

We knew that if you extracted part of the nervous system--just cut out a set of cells called the

bag cell neurons--and you ground them up, and you injected them into a second animal, that the animal would go through its stereotyped egg-laying behavior. That said, there had to be a chemical substance in those cells that triggered the behavior. It was known that this chemical substance--at least one of the chemical substances--was a short protein, a peptide, called the egg-laying hormone. So I set out to clone the gene encoding that hormone, and through understanding the organization of the gene was able to understand that the gene encodes more than one chemical substance that's important in producing the behavior.

We hypothesized that it's the concerted action of the set of these substances that are secreted from these neurons that produced the behavior. We understood then, as the years went on, how this protein is made, how the different chemical substances are packaged, and how the neural activity results in the secretion of these different substances, the physiological activities, and so on.

Hughes

Was it fairly well known then that a gene could express different proteins?

Scheller

Well, this gene made one protein, but then the protein, as it moved through the cell, was cut up into different pieces, and the different pieces were utilized differently.

Hughes

Was that known? Were there other organisms--?

Scheller

The other pieces of this gene were not known. It sort of was a hallmark of what was to come in molecular neurobiology, as in all areas of cell biology, that it's easier to work with DNA, and to understand cellular properties and molecular properties by manipulating the molecules through the DNA. That was really what we had done here in the nervous system, which I think showed people--again, something that seems obvious now--that the way to dissect the brain and the way to dissect things like behaviors at the molecular level was to use this great set of technologies of molecular biology to go in and pick apart processes.

Hughes

Because the technology at that stage was better for working with the DNA than it was with the proteins?

Scheller

Yes. DNA has four building blocks; it's a very sturdy molecule. You can't clone a protein. A protein doesn't reproduce itself; DNA reproduces itself.

Hughes

And proteins can have folding problems.

Scheller

Sure. One of the commonly accepted ways of studying all biological processes, including neurobiology, of course is through molecular biology. Back then, for a psychiatrist to think about DNA, and for a molecular biologist to think about behavior, that was the neat connection that was made.

Hughes

So you were calling yourself a molecular biologist by the time you got to Columbia?

Scheller

Yes, and then at Columbia a molecular neurobiologist.

Hughes

When did you become a molecular biologist?

Scheller

At Caltech.

Hughes

Because you were more and more focused on DNA?

Scheller

Sure, and I think that people use "molecular genetics," meaning gene cloning, interchangeable with "molecular biology." Molecular biology really includes biochemistry and non-DNA things, but, as I said, I think we probably agree that molecular biology really means to most people gene cloning.

Choosing Columbia for a Postdoc

Hughes

We dropped you at Columbia without explaining why you wanted to go there for your second postdoc.

Scheller

Although my first postdoc didn't really count.

Hughes

Why do you say that?

Scheller

Because I stayed in the same lab. I graduated so that I could get that out of the way, and then I could think about what I wanted to do and where I wanted to go. While I was thinking about that I'd be making a little more money; I'd be finishing up some projects. I know it's on my CV as a postdoc, but I didn't really think of it as an official postdoc, really just an extension of graduate school where I was getting paid a little bit more.

Hughes

Nobody said well, to get more experience you should graduate and find another laboratory?

Scheller

I'm sure that my advisor, Eric Davidson, would have been thrilled if I wanted to stay, but I'm sure that he would have advised me that it would be best for my career if I moved somewhere else. As I say, since this was planned to be relatively short--it really was just a bridging period--I don't think anybody thought very much about it.

Hughes

Why Columbia?

Scheller

Richard Axel is the person that I worked with along with Kandel. Axel is a molecular biologist and Kandel a neuroscientist. Axel had visited Caltech and presented some seminars, and I admired his work; I admired his personality, and it was for that reason. I had been exposed to him and his work through seeing him present seminars and reading his papers and so on.

Hughes

Did you go with a specific project in mind?

Scheller

Yes. Which is not the one that I did. [laughter]

Hughes

Well, tell me that story.

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Scheller

I don't even remember what my specific project was, probably to work on some aspect of gene expression. Axel had been sitting next to Eric Kandel on an university committee--both prominent professors at Columbia medical school. They began talking with each other and decided that they should collaborate somehow, but they didn't really know how. It was at that time that an issue of *Scientific American* on the brain came out just as I was leaving. I read that issue of *Scientific American* and became very interested in the brain.

Hughes

Had one of them written an article?

Scheller

No. This issue was written by several different people; Francis Crick was one of the people that wrote an article. So when I arrived at Columbia, Richard Axel and I began to talk about what I would really do. He mentioned that he had met Eric Kandel, and that he was a neuroscientist, and I very quickly became interested in that and went and talked to Kandel. It was a fantastic experience, really, because at the time Kandel did not really know what the gene was by the modern definition, and he certainly didn't know what recombinant DNA was, and so on. He was a neuroscientist trained as a psychiatrist. Richard Axel had never even seen an *Aplysia,* the organism that Kandel worked on, and Axel didn't know anything about neuroscience. They had very complementary techniques, and I was the person in the middle. It was terrific.

Interacting with Eric Kandel

Scheller

One of the great experiences in my life was Eric Kandel, last year's Nobel Laureate, teaching me neurobiology in his office, one on one; and I taught him molecular biology, one on one. So we taught each other what we knew about our fields. I think it served us both well.

Hughes

But your project was your project? He was somewhat at a distance?

Scheller

The question then was what to do. It was fine to say here's a molecular biologist, here's a neurobiologist, here's a kid in the middle; you still had to figure out what really you would do. I thought that I would make a recombinant DNA library of the genome of *Aplysia,* and in the meantime I would try to figure out what to do.

I was getting help dissecting the sperm duct from the animal in order to make the DNA from the sperm, from the germ line, and someone else was using other parts of the animal. Somebody was cutting out certain neurons, and I said, "What are those?" And the person said to me, "Well those are the bag cell neurons." And I said, "Okay, what do they do?" And the person said, "They govern the egg-laying behavior." I said, "Well, that's interesting." I'm thinking I'm a molecular biologist so the word "behavior" just intrigued the heck out of me. I said, "How do they do that?" And the person said, "We don't really know except that they secrete peptide hormones." That struck me as interesting because peptide means chains of amino acids, which means there must be genes for these. I said, "What do they know about these hormones?" And he said, "Not very much. They know the protein sequence."

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Scheller

Remember, I said before that the cell makes a large amount of one particular thing. Then it can be relatively easy to isolate the gene. Well, there weren't very many of these cells, maybe a few hundred per animal, fifty microns in diameter. So from relatively few animals I could obtain enough radioactive cDNA that I could then screen the genome library and find the pieces of DNA in the genome that encoded the gene for the hormone. For a well-trained molecular biologist this was a breeze.

Hughes

And you did do that very fast?

Scheller

Yes. We published two *Cell* papers and a *Science* paper in a year and a half. [5] #13, 14, & 17 in Scheller bibliography. Then I left. I often look back and wonder where I would be if that scientist wasn't dissecting those cells. He heard we were going to have some big animals because [we were] getting sperm to do the recombinant DNA, and he wanted to use some other parts of the animal, and I just happened to ask him, "What are those?" Where would this have ended up if I hadn't asked that question? But I did.

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II Faculty Member, Stanford, 1982-2000

Assistant Professor, Department of Biological Sciences

Deciding on Stanford

Scheller

I think then what happened happened a little fast. They wanted me to join the faculty at Columbia. I was very honored by that. But in the same way that I think it's a good idea to move away when you do a postdoc from the place where you've done your undergraduate work, to move away from where you do your postdoc is also important so that you can strike out on your own. And since they had offered me a job at Columbia, I thought that I should look for jobs other places in the country, and if I couldn't get one anywhere else then I would stay at Columbia. It wasn't that I didn't like the people there; it's just that I really felt very strongly that I needed to strike out on my own and was fortunate enough to get a position at Stanford, which is where I moved.

Hughes

Were you offered any other positions?

Scheller

Also at MIT.

Hughes

And why did you choose Stanford?

Scheller

I wanted to move back to California. I like California; I had lived in southern California; I had visited northern California. I didn't mention this: One of the first things I did when I moved to California from Wisconsin was to fly up to San Francisco. I think I delivered some linkers to the UCSF group and then hitchhiked from San Francisco to Los Angeles, camping at Big Sur for a few days, and so on. I had very fond memories. That's when I was probably first exposed to poison oak, which I'm very allergic to now. Also I had very fond memories of northern California.

Hughes

Did you have any particular connections with Stanford?

Scheller

No, but certainly my former mentors at Caltech and at Columbia knew people at Stanford and were very supportive of my getting a position there. So I came out and interviewed, and one thing led to another, and I ended up spending almost twenty years there.

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Hughes

Your position was first on the general campus, as opposed to the medical school, in the department of biology.

Scheller

At first. The work that I did on the marine snail in neuroscience fit in with the kind of vacancy that they had there. Also, both Davidson at Caltech and Axel at Columbia had very close ties to the chairman of the department at Stanford then, who was Robert Schimke, also a prominent molecular biologist. Certainly, I think those kinds of connections speak volumes for getting your foot in the door. Of course you have to come and perform.

Corey Goodman as Colleague in Neurobiology

Hughes

Was Schimke a neurobiologist?

Scheller

No, but there was another scientist there who was a young star in the department at the time and a more classical neuroscientist then; Corey Goodman was his name. He was interested in having a colleague in the department that was a molecular neurobiologist. He felt that neurobiology was the future of biology because that's what he did. He thought that we could share techniques and collaborate, and so on. So that would be the kind of colleague that he would like to have, both for the good of the department and for the good of his own work.

Hughes

He wasn't a molecular biologist?

Scheller

No. He was a more classically trained neuroscientist. He used morphological techniques--microscopy, electron microscopy, and electrophysiology--to study the development of the nervous system, in particular how the complex circuitry, the wiring of the brain, arises. He had defined that in classical systems like the grasshopper but then wanted to study this at a more biochemical and molecular level, using fruit flies and recombinant DNA, and so on. When we met, he was merely thinking about making the transition from the more cellular studies to genetic and molecular work. I hit it off scientifically and personally with Goodman and Schimke and other people in the department and accepted the job there.

Hughes

Did they have other people that had the skills that you did, with the heavy background in molecular biology, or was that what they wanted?

Scheller

There were other people there: Schimke himself, Charles Yanofsky was in that department (one of the fathers of molecular biology), and Alan Campbell who studied recombination in bacterial viruses, phage. So there certainly was a strong group of molecular biologists there. I suppose you would have to ask them, but I didn't think that they had ever dreamed of studying the nervous system with molecular biology.

Hughes

Because it seemed so complicated?

Scheller

It also just wasn't what they worked on.

Hughes

So you were bringing a new interest to the department.

Scheller

Sure. The way I had applied molecular biology was novel. I think everyone in the department recognized that this novel way of applying molecular biology would result in a lot of interesting discoveries over the years. That's the kind of person and the kind of research program that they would like to have in the department.

Hughes

The novelty being the behavioral aspect?

Scheller

The behavior and the analysis of the behavior at the level of genes, and molecules, and cells.

Hughes

Was there anybody else anywhere doing that kind of research?

Scheller

I'm not sure. I certainly don't think there was anybody that was talking about it so explicitly.

Continuing Research on Molecular Development in *Aplysia*

Scheller

I continued the work on genes and cells and behavior for several years at Stanford, moving onto other neurons. We were able to dissect individual nerve cells, the bag cells that were clusters of maybe fifty cells or so. I had to get a game permit. We would go to the Elkorn Slough south of San Francisco; we would collect *Aplysia* after they had laid their eggs so that there would be a new generation. They are annual organisms, so they were destined to

die anyway after laying their eggs. We would bring them back to Stanford and dissect the nervous system, pin it in a dish, and people would dissect the individual nerve cells and call out that they have an R2, or an R14, or an L11. Someone else would come with a tube and place the one individual cell in the tube so that by the end of the day we would have a set of twenty tubes, and in each tube would be 200 individually dissected nerve cells. We could then characterize the genes that were expressed in those specific cells. Coming back to what I mentioned earlier, we were able to do that because the cells were large enough. We had to use microscopes, but you could relatively easily dissect them and work with them.

Hughes

Doesn't this take tremendous dexterity?

Scheller

I don't really know; the students did that. I got the dirty work; I had to pin the animals down and open them up and dissect their brain. Then the students would do the individual dissections. So I had to roll up my sleeves and do the heavy-lifting work. It was fun. We had pizza for lunch and then got back to it. It was a tremendous group effort to do that because we didn't maintain the animals. We would collect hundreds of them in the morning, drive back to Stanford, dissect the cells, and be finished by the end of the day. This was a long day, but you basically had to do it all in one day.

Hughes

How often did this happen?

Scheller

This would happen periodically, a few times a year, and then we had 200 of twenty different cells, all in the tubes. Studies of those then would take weeks and months and years. We would clone the genes for the neuropeptides that were expressed in the cells and then try to

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understand what those genes did--how they functioned in other aspects of the animal's behavior.

Hughes

These were graduate students and medical students?

Scheller

These were graduate students and postdocs and M.D./Ph.D. students (the students involved in getting both degrees). There were probably a few medical students involved.

Hughes

I asked that question because one of the emphases of Stanford's medical school curriculum at one stage was to get students into basic science laboratories.

Scheller

That's still the case. At Stanford, in particular, many medical students take five years to get their M.D. and spend a year doing research. Many times the medical students really don't have the amount of time to put in to do a sophisticated, in depth, research project that would take three, four, five years. That's of course a generalization; it's not necessarily true for any individual. But it's hard to go through medical school and do research at the same time, which is why we have a M.D./Ph.D. program at Stanford where you do two years of medical school, three or four years as a Ph.D., and then your last two years of medical school, which are mostly spent in the clinic.

Department of Molecular & Cellular Physiology (1990-1993) and Howard Hughes Investigator (1990-1994), Stanford University Medical Center

[Interview 2: September, 21 2001] ##

The New Appointments

Hughes

You were in the department of biological sciences, and by 1990 you had moved over to the department of molecular and cellular physiology. Is there a story there?

Scheller

An age-old story--money. [laughter] The Howard Hughes Medical Institute had funded construction of the Beckman Center at Stanford, and the Beckman Center housed two new departments that were endowed with Howard Hughes professor positions. I had been recruited to be on the faculty at some other universities that were offering me Hughes positions, as we called them, which amounted to about a million dollars a year for your research. Of course I was very attracted. I think in part to retain me on the faculty at Stanford I was offered a Hughes position.

At the time these positions had to be affiliated with a medical school due to the complicated organization of the Howard Hughes Medical Institute. So I left biological sciences, moved across the street, and became a Hughes professor in the physiology department. I maintained an affiliate position with biological sciences and remained close to a number of the faculty there, such as my wife Susan McConnell. [laughs] I'm still close to a

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number of the people in biology, which really gave me my start at Stanford. In a way, that's why I say "for the money."

Hughes

Did it make any difference that you were now in the medical school in terms of what kind of research you were doing or in any other way?

Scheller

Not really. I don't think it changed a lot. I had begun studying membrane trafficking and synaptic transmission and the mechanisms of membrane fusion while I was in biological sciences. I have to say that the money made a big difference. It allowed me to recruit more people. It allowed me to take more chances, to do experiments that I might not have otherwise done because I had to rely on more conservative routes for funding my work. In a way it's sad but true that the money really did make a difference in the research that I was able to do. The department I was in didn't matter as much.

Hughes

I was wondering about changes in facility interactions, but of course if you were in biological sciences right across the road that wouldn't have made a big difference.

Scheller

I think it probably did affect things in ways that if I thought real long and hard I could come up with. The people you run into in the hallways are the people you exchange most ideas with which do affect the work, specific experiments in particular, that you end up doing, but often not in ways that are so easy to pinpoint. I think the point is, both environments at Stanford were outstanding, and I enjoyed both of them.

The major difference is that the physiology department was focused on issues of neurobiology and synaptic transmission. There were eight faculty, and everybody worked on that. And that was good; everybody lived and breathed that science. It was stimulating. In biology there were thirty or forty faculty members, and they studied everything from bacterial viruses to human-population biology and ecology. It was a much more diverse department, so the interactions there were fun in that it often stimulated you to think about things outside of your field. But the interactions were not as stimulating for thinking deeply inside your own field. Those were the major differences.

Scheller's Wide-ranging Interests

Hughes

I talked briefly with Professor [Charles] Yanofsky when I knew I was going to be talking with you. He admitted that he didn't remember too much about the ins and outs of your research, but he did remember seeing you often at seminars on a wide range of topics. Is it characteristic of you to have broad interests?

Scheller

Sure. When I was a student at Caltech, it was possible to understand pretty much everything that was going on in biology. To even say that to a student nowadays would flabbergast them because there's so much going on. I felt as though twenty-five years ago I knew everything about what was going on, and I've tried to maintain that knowledge as much as possible in the intervening years. Although of course it's become impossible; it's still fun to try.

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Corporate Consultations and Comparisons of Academic and Industry Science

Hughes

Were you in some way, either conceptually or by arrangements, maintaining connections with the commercial aspect of the science?

Scheller

I think you're going to be a little disappointed there. [laughter] Not very much. I consulted for a few companies, and I mostly did it for the money. My salary at Stanford was comfortable but it certainly wasn't lavish. Stock options and $1500 or $2000 a day consulting fees were extremely attractive.

To be honest with you, I wasn't particularly fascinated with the science that was going on in industry. I was more fascinated by the cultural differences, the ways that decisions were made, the factors that were taken into

consideration in making a decision. I really did enjoy the cultural differences between my own lab at Stanford and the biotechnology industry.

Hughes

Please talk about that.

Scheller

Well, you had not only to think about whether the experiment would work; you had to think about was there really a medical need that you were eventually moving towards. What would the product be? How long would it take to get the experiment done? What outside investors would think of this area? Those types of issues were never factored into our thinking at all at Stanford. I found the decision-making process and having to factor in those issues curious and, because of their novelty, interesting. But the science that people were trying to do, to be honest with you, was really not particularly fascinating to me; it was superficial compared to the things that most people were working on at Stanford.

Hughes

Partially because of having to draw research towards application?

Scheller

Yes, having to make it an applied project. In general the scientists were good scientists, but they weren't given the opportunity to think as freely and as deeply. Their goals were set very clearly, and they were in a way asked not to think outside the box [but rather] to move towards those goals at any cost and not to get distracted. Whereas at Stanford we liked getting distracted by things that were interesting, and it didn't matter whether they had anything to do with the potential project or not.

Limitations on Outside Activities Imposed by the Hughes Institute

Hughes

Did you ever have any interest or involvement in the social and ethical issues that have been raised for decades over the possible impact of commercial interests on the way academic science is conducted and the way academic institutions behave?

Scheller

Fairly little. The Howard Hughes Medical Institute was extremely restrictive and rigorous in that respect, and we were quite carefully monitored in terms of our consulting arrangements. We were very carefully monitored in terms of our licensing agreements, our ability to

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distribute reagents, and so on. The institute is tax-free, public. The endowment is held in the public trust. They have to be very careful. I was a direct employee of the Howard Hughes Medical Institute. They had to be very careful to make sure they were squeaky clean in that respect, particularly given their somewhat shady past.

Hughes

How did they look upon your consulting?

Scheller

They had a maximum amount of stock that you were allowed to have; they had a maximum fee per day that you were allowed to charge, and so on. It was quite, I thought, unfairly restrictive.

Hughes

And time restrictions as well?

Scheller

Stanford was one day per week, and the Hughes, I think, was twenty-eight days per year, something like that. It was again quite carefully monitored. The Hughes, being more restrictive than Stanford, was quite unfair, and in a way put the Hughes investigators at a personal financial disadvantage compared to other scientists that had more freedom to consult. I thought that the Hughes shouldn't worry about how many hours you spend doing things and that they should judge you on your science; you're either good enough to be a Hughes investigator or you're not. If you don't come into work at all, and you somehow got the job done, more power to you. [laugher] Overall, the Hughes was very good to me, and supportive, so these were minor things.

III Director of Scientific Research, Genentech, January 2001-Present

Decision to Join Genentech

Need for a Change

Hughes

That then begs the question, why did you come to Genentech?

Scheller

There are a lot of reasons. I think that the main reason, and I would say 99 percent of the reason, is that I just wanted a change in my life. I wanted to do something different. I wanted new challenges. The academic life is absolutely terrific. I could have very comfortably spent another twenty years at Stanford being a researcher and been extremely happy. I think that needs to be made clear--you'll see why.

The main thing was just for a change and for new challenges. It had become easy to be a professor at Stanford. I got good students; we did good experiments; we wrote papers. Sure I could have been doing better, I suppose. I could have made more important discoveries, but I was doing fine. It just wasn't as much of a challenge as it was when I was getting started. I wanted new and different challenges.

Criticism of the System of Scientific Publication

Scheller

Having said that, I was also fed up with the system of publishers. What you do to publish a scientific paper is to work for weeks, months, years, to collect the data, to analyze it, to understand it. Then you send it into a journal. Editors of the journal then judge whether your work is important enough, novel enough, to be considered for review. The editors, of course, know much less about the field than you do. They're really not in any kind of a position to make these decisions, but they make them anyway. Then the papers are sent out to your "colleagues," and I think most people try to produce fair and rigorous reviews. It's become standard in the field for people to feel as though they need to be extremely critical of papers, both technically and whether something is "interesting" enough to warrant being published in journal X versus journal Y. The paper is often rejected, or it needs much more work, or it needs this or it needs that in the opinion of someone else. Some of the feedback was very useful; often most of it was either not useful or not realistic. So you get into a battle with the editor and a battle with the reviewers, and this would go round and round.

You know what? I got sick of it. I just didn't need it. I just wasn't interested in that anymore. I think it's a sad thing because as you know from the interview that we've done all I ever wanted to be was a scientist, and I feel as though the system took the fun out of it for me. The system doesn't owe me anything, but I'm a little bitter about the system. It's as though it took my childhood dream away from me and made it so that it wasn't fun anymore.

It wasn't even so much me. I was successful. I was a professor. I couldn't be fired. I was doing fine. But to try to explain to a student who had worked for years, who wrote what in our opinion was often a very nice paper why their work wasn't going to be accepted or published-- I didn't think there were really any good reasons. You had to look this kid in the eye and explain to him. It was extremely painful to me, to where I got to the point where I'm not sure that in good conscience I would recommend to students that they should become academic scientists.

Hughes

That's sad.

Scheller

I thought, what am I doing here? I agree with you that it's sad. It's gotten so competitive; it's gotten so political. Academic scientists are often very motivated by prizes--the Nobel Prize, this prize, that prize. Publishing is the way to move up the ladder towards those prizes, and it got to the point for me where I just didn't want anything to do with it anymore. That's too strong a statement. I still publish papers. It's not that I didn't want anything to do with it. I wanted other things in my life that were as or more important so that I had other things to think about--other diversions, other interests, so that it wasn't so deeply important for me to have my scientific discoveries published in this journal or that journal.

It's even worse than that. So you send the paper in; they often send it back rejected. You work for the journals for free as a reviewer. They send you papers. You work many hours studying them and writing critiques. You don't get anything for that so you're working as a slave for free. You pay to publish the paper--you pay page charges. If you have a lot of color figures sometimes it's thousands of dollars. [voice crescendoing] And then you pay them to subscribe to the journal! [laughter] They walk all over you: you work for free; you pay to publish; and then you buy the journal back. What kind of a system is that? Man, they have got it made, I'll tell you. Anyway, that also was part of [my decision to join Genentech].

I also felt that the scientific conferences were such a big part of science. I enjoyed traveling all over the world and meeting with people. But I found that when I accepted the job at Genentech, I canceled sixteen meetings that were all going to be fun and interesting, but I wasn't really going to learn that much at these meetings. Maybe I could do more good using my talents somewhere else, other than meeting with my colleagues and discussing the last couple of weeks' worth of data where things really hadn't changed that much.

Seeing Opportunities at Genentech

Hughes

What did the Genentech position offer as a counter to these problems?

Scheller

Again, I want to stress that it was 99 percent just wanting a change. I was not unhappy at Stanford, as I said. I wouldn't have taken just any job. I think there probably wasn't any other job, in the Bay Area at least, that would have been exciting enough that I would have left Stanford. This was a real opportunity. Look, Genentech is a great company, and it's a great place to work. I have to admit, it's very different coming from a lab where you have twenty students and postdocs to being head of research where you have 520 that you now supervise,

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or a building where you can now hire 400 more people, or you're on an executive committee that runs a billion-dollar corporation. In a way I feel it's a little bit like other phases of your scientific career; you move on to the next phase where you're doing a number of things that you were absolutely never in any way trained to do. [laughs] But you either manage somehow or you're not very good at the job, and you don't manage.

Hughes

Presumably you were thinking about all this before you accepted the position.

Scheller

Well, sure. I knew that I would be interacting mostly with scientists, and I think that I have an appreciation of what scientists are like, how to talk to scientists, what's important to scientists, and so on. I thought that I could be a good scientific manager on a larger scale.

Establishing Goals with Arthur Levinson

Hughes

What about doing the kind of science that you were describing when we first started this conversation today--a more circumscribed, applied kind of science?

Scheller

That's right. We have very specific goals, and that's one of the things that I discussed my first week here with my boss, the CEO of the company, [Art Levinson]. He gave me written goals, and I looked at them, and I never had anybody write goals for me before. I discussed with him how much I really could affect whether I accomplished these goals or not and what it really meant to have goals. My attitude really was, look, I'm going to work hard, and after that it's sort of up to fate whether I accomplish these goals or not. He in a sort of general philosophical sense agreed but thought that it was extremely important to be clear what he was expecting from me. To write it down so that we each had a copy brought that clarity to what he was expecting. So I have my goals, and I'm working on them. [laughter] Let's put it that way.

Hughes

How is it after decades of pretty much being your own master having somebody to whom you have to report?

Scheller

Well, I do have to report. I also have a lot of freedom and a lot of latitude at Genentech. I'm in charge of research, and I essentially make the decisions about the directions that we're heading in research. The fact is I like my boss. He was the head of [Genentech] research years ago, and we get along extremely well, so it doesn't really feel like a constraining relationship in any way. It feels more that we're working together towards common goals than that he tells me what to do and I go do it.

Hughes

Does it also make a difference that Art's origins are academic?

Scheller

It makes a big difference that his origins are not only academic but mostly scientific. So if there's an issue, I can explain the facts to him, and we can analyze it using a shared set of analytical principles that are the scientific method that we share because of our backgrounds. I think that helps tremendously.

Hughes

Yet as CEO his role is predominately that of a businessman, while yours is as director of science.

Scheller

Yes, although it really is all related. Some people at Genentech think about how much money we make. Another way to think about it is how many patients we help. They really go hand in hand.

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Scheller

You can think of it in terms of patients, not dollars, and if we help a lot of patients we will make a lot of money. The way to help a lot of patients is to do good research, to be good medical scientists, and to discover important therapeutics. Maybe I'm still idealistic since I've only been here six months, but the fact is our country is set up in a way such that the fruits of basic scientific research are brought to benefit mankind through private industry. It seems to be as good a system as any that I've seen in the history of the world, and that's the way it works.

Hughes

So putting the patient into the equation was a draw for you?

Scheller

[hesitantly] Yes, it was a draw for me, but I didn't see that I was trying to do anything particularly profound in terms of changing the world. As a professor at Stanford I was more or less just trying to stay busy and lead a good life. It's really the same. Sure, it's nice to think that we're going to help patients, but at the same time I don't-- [pause] I don't really think of it daily in terms of that deep motivation. It's more just getting up in the morning and doing something interesting to keep myself entertained and of course to lead a good life. But I don't wake up thinking, "I'm merely awake now to go help people." I'm just here to do good science--again, science with a different set of decision-making parameters than when I ran my lab at Stanford.

Research to Produce Products

Hughes

Talk about how those parameters are different.

Scheller

Those parameters involve working on projects many of which have the potential to lead to treating unmet medical needs, rather than just anything that happens to be interesting, or any direction that you happen to go. What we're trying to do here is much harder than what I was trying to do at Stanford, and that's what a lot of people find hard to believe. They think, gees, professor at Stanford, that's a hard thing. The difference is really what I've mentioned already: At Stanford just so I discovered something kind of cool; it didn't really matter what it was. Here you can discover something kind of cool and that's valued, but you're really much more rewarded for discovering something that leads to a medical breakthrough. It can't be just any interesting thing that happens. And that's what makes it harder. And that's what makes it often necessary to stay more focused on a particular path and not to go off on tangents that could just be interesting but wouldn't really lead you to the medical breakthrough. It's as if we have to discover something specific rather than discovering just anything, and that makes it harder.

Hughes

Has it yet happened that you've been on to something scientifically interesting that didn't have a clear application and you had to cut it off?

Scheller

[hesitantly] Well, sure. At Genentech there's enough latitude that if it's interesting scientifically we'll usually pursue it at some level, and that's one of the reasons that I would have only moved here versus other places. Some of the small companies, their company is on the line--we're talking the difference between having a company next year or not. There often isn't the latitude just to do some interesting science. While I try and keep things focused here, I also encourage all of the scientists to have applied and a more basic research project. The hope is that some low percentage of the basic research projects will result in technologies for the future that end up being valuable for the company in away that we can't easily predict today.

Dealing with Genentech's Culture

Scheller

I walked into a situation where there was a culture that had evolved over twenty-five years. Many of the scientists felt entitled to that culture. They felt entitled for the culture to go on the way it's been for the last number of years that they've been here, and they didn't want any change.

Hughes

How would you define this culture that they wanted to retain?

Scheller

I don't really want to get very specific about it, other than to say the way they do things and what they expect the company to be: The way they expect to make decisions, the way they expect to be treated, the way they expect the decision process to be made, the size that their office should be, the pay that they should have, the scientific directions that we should be moving in--just a whole long list of things that have become ingrained in the culture

here that didn't necessarily fit my vision for what the culture should be. There are 520 employees and one of me. [laughter] But I get to make the decisions.

Hughes

So how are you doing?

Scheller

So how am I doing? Well, I'm still here. [laughter] A number of people have been extremely helpful. [Genentech] human resource people have helped me with some of these issues.

I'll give you an example: Desks and where they should be situated. At Stanford all the desks are in the lab. Every place I've ever worked the desks are in the lab next to the [lab] bench. Here, postdocs and RA's and senior RA's--an RA is a research associate--have offices. We're building a new building. We broke ground on the building, and I looked at it and I said, "The offices are over here and the benches are there. I want the desks next to the benches." People had a fit. They felt as though something that they were entitled to was being taken away from them. They felt that it was being done so that I could watch people more carefully that I didn't think were working hard enough. They thought that it was being done because maybe then the senior RA's that were paid a lot would quit, and I could hire junior people and save money. The fact is, I just don't think that way. I put the desks next to the bench because

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if you're doing experiments you should want to have your desk next to your bench where you're working so you can go back and forth and it would be easier.

So this led to my first and one of my most dramatic sets of conflicts of culture with people here. We reached what I suppose can be called a compromise. As I said, I had a lot of help from the human resource people at Genentech in organizing town hall-like meetings or working groups to discuss how this would be potentially organized.

Hughes

Where are the desks going to be?

Scheller

They're in the lab, but they're now called "attached offices," and there's a sliding glass door in between the desk and the bench, which is a perfectly reasonable compromise.

Fostering Scientific Interaction

Hughes

Well you know, historically you're on the right track. Dave Goeddel told me it was Swanson's preference to have scientists working in close proximity to force interaction.

Scheller

Absolutely. Now we're so big and we're so spread out that there are people here that don't know other people; there are people here that never run into each other. I've tried to foster greater interactions between the different departments. Now people at Genentech can have joint appointments in more than one department in order to foster that interaction, something that's commonly done in academia but had never been done here.

Hughes

How are people taking to that policy?

Scheller

Oh, they think it's absolutely terrific.

Hughes

Do they spend time doing research in different areas?

Scheller

They've usually been collaborating at some level before. This is a way of formalizing it so they now come to the seminars and the luncheons and things like that. They remain in the same physical space but they have a tighter connection to departments other than their own as a way of formalizing the fact that they're working together, not within a department but often between departments.

Hughes

Is Genentech like other bioscience companies in having a division of activities?

Scheller

Yes and no. A lot of biotech companies have labs more like Genentech's. But, a lot of the newer facilities that are being made are going back towards the academic models as a way of instilling the idea that in part the reason

we're here is to be doing experiments, and you shouldn't want to have your desk anywhere other than next to your lab bench, because that's where you should be.

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Scientists at Genentech and Stanford

Hughes

Please compare the quality of scientific discussion and communication at Genentech with what you were used to in academia.

Scheller

In academia and in industry there's a huge range of scientists, some of whom are the best in the world and others of whom are not as good. I find that here at Genentech, and that was also the case at Stanford. The quality of the science here is excellent. The level of discussion is just as deep. I think there are probably on the average more creative scientists at Stanford than at Genentech. I don't think there are more at the level of creativity of the best people here. The best people here are really the same as the best people at Stanford. They're terrific people both places.

Scheller's Recruitment

Hughes

Tell me about the recruitment process. What were you told you would be doing, and how did that jibe with actuality?

Scheller

Well, on my first visit I met with Art Levinson, the CEO, and with Dennis Henner. Dennis, in particular, described the organization of research and the goals of putting molecules into development to become products. Art Levinson talked more generally about the philosophy of the company--helping with unmet medical needs and so on. I think all of those very general issues jibed very closely with what I was told. Nobody could prepare me for the more detailed issues, but the general expectations of what I would be doing and what I was expected to do were very fairly portrayed by Art and Dennis.

Hughes

What did they see in you? Why did they want you?

Scheller

I think they wanted first and foremost a good scientist, and a scientist that the other scientists would respect. That was very important. You needed to have a scientist of a certain level of accomplishment that could come into the group, otherwise you'd have a lot of people wondering, why is he the boss? Maybe even so you'd have a lot of people wondering that and wondering, why aren't I the boss? So those 250 papers and a membership in the National Academy and so on were very important credentials that Art Levinson could hold up in front of the group of scientists here and say, "Look, this is a good scientist. This is someone that knows how to do science, and that's why I'm hiring the person, and that's why you should respect him." Your publication record's almost the universal language within science. Other scientists can look at your CV and see what you have accomplished and then judge for themselves whether your career has been good, bad, indifferent, outstanding.

Hughes

Did the discipline in which you had achieved, neurobiology, have any significance?

Scheller

That was probably a negative if anything since Genentech really doesn't work in neuroscience. The techniques that are used by scientists nowadays and the basic ideas of

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molecular biology and cell biology are so similar among different disciplines that the logic, the thought processes, are shared among all disciplines. It didn't help me to be a neurobiologist, but apparently it didn't hurt too much since I'm here.

Hughes

Genentech came to you rather than the other way around?

Scheller

Genentech would never advertise a position like this, and even if they did I would never apply. So yes, they came to me.

Hughes

Had Genentech gotten word that you were restless?

Scheller

Sure, they had heard from their scientific board, probably through David Botstein at Stanford, that I would consider other opportunities. Then Art Levinson checked with other people, like Richard Axel who's on the board who I worked with as a postdoc; and with other scientists as well. I know everybody that's on the Genentech board, so it was interesting that Art really could have called anybody, and they would have known me at different levels.

Hughes

It sounds, the way you tell it, that your status in science was important to Genentech more for internal reasons than for external. Did they want to advertise you to the external world as an accomplished scientist?

Scheller

They certainly did advertise [my appointment] to the external world. I think that was very important as well. They would have been embarrassed to put up the name of somebody that hadn't a long list of accomplishments that they could list after his or her name. That was certainly expected and that was certainly touted in the press releases and so on. That made Genentech feel proud and accomplished that this was the kind of person they were hiring. So I think that my appointment was very important for both internal and external purposes. Although it certainly didn't make such a difference that hiring someone to run research instantly affected the value of the company in any way. I think no matter who it had been, the response of the business community is, okay, fine, now let's see what the person can actually do. I'm not going to increase the value of your stock because you hired some guy from Stanford. Let's see the medicines that come from this guy; then I'll pay more for the stock.

Dennis Henner and David Martin, Previous Directors of Research

Hughes

Was there a passing of the wand from Dennis Henner in terms of philosophy or culture? Does the director of research position have its own traditions and standards?

Scheller

I think there's quite a bit of difference between Dennis Henner and myself. Dennis had worked here for twenty years. Dennis never had an academic career. He came here, I think, after a postdoc, and his whole professional career was at Genentech. It's fair to say that most people would consider Dennis a good scientist but not a very accomplished scientist. There were other scientists, like Dave Goeddel for example, who would have been considered very, very accomplished scientists, all from work they'd done at Genentech. We also brought a different philosophy to how we do science, how we think about scientists.

Hughes

Dave Martin came to Genentech directly from academia, just as you did, to become director of research. How could he help but carry the academic culture with him?

Scheller

Sure. Also with Dave it was a very different company then. That was fifteen years ago or more. Genentech was much smaller; it was much more of a free-for-all; it was much less organized and much less focused on a few different areas and so on.

By the way, I don't think that my culture is better than Dennis Henner's; it's just different. We'll see whether one or the other is more effective, or whether they were both effective but just in different ways.

Hughes

How do you think that Levinson's goals are going to interact with the academic cultures that you bring with you?

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Scheller

Genentech's goals will be best achieved by doing very creative science.

Genentech's Openness about Science

Hughes

What was a surprise to you?

Scheller

[pause] I've learned a lot about business from the executive committee meetings. The [executive committee is composed of] six people that fund the company, the CFO [chief financial officer], the head of legal, the head of operations and sales, the chief medical officer, and Levinson. I've learned a lot about the legal system.

There have been two things that were really surprising to me about the science. We are more open here about what we're working on than in academia, which is exactly the opposite of what I thought it would be.

Hughes

You mean open to the outside world?

Scheller

About the projects that we have going on, the progress we're making on the projects. If I was doing something at Stanford, I wouldn't tell anybody until I was really secure that this work had found a home in a journal or it was going to come out where I was going to get credit for it. I don't know why that is here, and I still disagree some with that philosophy of Genentech. I think that we should be less open. I don't see any reason to tell the world what we're working on. I don't see any reason to tell our competitors, in particular, what we're working on, how far along we are, what kind of data we're getting. It seems to me to put us at a disadvantage by telling everyone, yet it seems to be the culture here. I'm not sure if that's because we're a publically held company and we owe it to our stockholders to inform them about what we're doing. I personally think that it would be in the best interest of the stockholders if we said less about what we are doing.

Intellectual Property in Biotechnology

Gene Patenting

Hughes

What about the role of intellectual property protection? If Genentech patents its discoveries, then one could argue that you don't have to worry about talking about them.

Scheller

That's the other thing that has surprised me. The intellectual property situation revolving around genes, in particular, is so unbelievably complicated. When I came, I preached to the executive committee that the whole genome was being divided up, that people were picking genes that were theirs, and that was going to be it for the next twenty years. So we had to hurry.

While I was preaching that we had to hurry, it was over already. There are so many patents on so many genes that I think it's very bad for the industry in general. Somebody might own the composition of matter--that is the protein encoded by the gene. Somebody else might own the utility around what that gene might be useful for. Somebody else might own the actual antibody raised against the protein and have shown that the antibody actually does something. By the time you divide it all up there's nothing left; there's no incentive for a company to work with these genes. There's so much intellectual property revolving around the genes that make up the building blocks of animals. It's extremely complicated; it's extremely frustrating; and I think that it's extremely bad for the industry and for the future of medical discovery. It also was a surprise and a bit of a shock to me how much intellectual property there already was around the genome.

Genentech certainly has its share of that. We certainly have been a player there. We have our chunk of property that we'll defend and trade and barter and use for our own business and for our own discoveries. But in the end, my god, somebody needs to actually make the drugs and to be able to profit and benefit from that. The way it's set up now it's not so clear how that's all going to unfold in the coming decade. Your question really brought me to the second big surprise that I had about the way things were done here. If you're in academia you just work with a gene; you publish your paper; you don't care if somebody owns it. You make it and publish it; who cares who owns it!

Hughes

Issues such as this go back to the very beginning of commercial biotechnology. There was a furor over the Cohen-Boyer patent application, for example, the first major patent in biotechnology. What's happened recently is that the tremendous activity around the human genome has made the problem more complex and more visible.

Scheller

That's what I'm saying. You need to have patent protection in order to protect your company's investment in the project, in the science, in order to recover a profit, hopefully, from the medicine that you make, and to recover all of the tremendous research and development expenses that went into discovering and developing the medicine. But that's been taken to an extreme where people do projects to capture intellectual property and just stack it up and then say, "If you want to make a medicine you have to go through me." You don't just make the medicine and then say, "All right, now I've done it; it's good for mankind. Now protect me so

I can recover my investment and be a good company." You just stack up intellectual property and prevent people from doing things, trading with people: Have somebody discover, have somebody make a medicine, and then

come around the back and say, "By the way, I own that. I know I didn't put much work into it, but look at this piece of paper I have; a chunk of it is mine." That's good business but it's not good for mankind, in my opinion.

Hughes

And it ultimately isn't good for business if each company has only a tiny piece of the pie.

Scheller

And it's all split up in complicated ways, and the legal fees continue to increase and then skyrocket, and everybody's suing everybody else and round it goes.

Hughes

What's the solution?

Scheller

You just move forward and do the best you can. I think that one of the things that will happen is that medicines will be more and more expensive. That's a given outcome of all of this. I think there will be cases where certain medicines aren't made that could have been made that would have helped people. There will be a proliferation of the legal issues in the industry. We'll move forward and do the best we can.

Hughes

Why can't there be correctives in the patent system itself?

Scheller

I think there have been to a certain extent. I don't think people are issuing patents on DNA sequences alone anymore, so there are attempts to correct the system as we move forward. But what you do then is have the DNA sequence and find out its expression pattern in a disease versus a normal tissue and propose the utility based on that. So the system corrects itself, and then science adds a little bit more to allow a patent, and then that may correct itself again; then we'll add just a little bit more to that. So you can always find ways to seemingly stay one step ahead of the correction. [laughing]

Hughes

Do you hold patents?

Scheller

I might hold one or two from my work at Stanford but nothing that's particularly noteworthy, unlike most of the scientists here.

Hughes

Stanford has the reputation of being quite entrepreneurial in terms of the commercial value of research done by its faculty. And Columbia is no laggard. Please compare the emphasis on practical application at Columbia, Stanford, and Genentech.

Scheller

As we've said already it's night and day. At Stanford and Columbia and Caltech nobody really cares if there's a practical application. If there is, the patent offices of the universities are anxious to capitalize on it, but it's not the goal. Here patenting's one of the goals.

Emphasis on Patenting at Stanford and Genentech

Hughes

American research universities in general have become much more appreciative of patenting opportunities. Say twenty years ago, Stanford was probably leading the pack. Were you aware of that culture?

Scheller

Sure, but 99 percent of the discoveries that are made at Stanford the patent office was uninterested in. You say, "I have a discovery; it's this gene." Stanford would say, "Look, it will cost us $40,000 to patent something, and is anybody really going to be interested in that?" They would send out queries to companies and say, "Would you be interested in licensing this?" If the answers didn't come back "yes," they would not pursue a patent. Whereas here we're happy to patent 600 genes--many of which people may not want; where we don't know what they do--with the thought that longer term a discovery will happen that will make this intellectual property valuable.

I think the other thing about patenting--the kinds of patents that happened to come from places like Stanford and UCSF (recombinant DNA) or Columbia (gene transfer into cells) were very fundamental technology-type discoveries of twenty years ago or so that were then very broadly licensed for a very reasonable fee. Stanford charged a few hundred thousand dollars to license the Cohen-Boyer patent. This wasn't restrictive in any way,

whereas companies may use patents to completely block another company from doing something. So patents can be used in a much more aggressive way by industry than by academic institutions. I think that's understandable. It's in the best interests of the companies today. It's not necessarily in the best interest of mankind.

Scheller's Programmatic Changes

Hughes

Have you made programmatic changes since you've been at Genentech?

Scheller

Oh sure. That's another thing: If your project is discontinued and you're separated from the company, you're not necessarily very pleased with me.

Hughes

I can imagine.

Scheller

I can imagine that too. It's not an easy thing for me to make these changes either, but it's something that one needs to do based on where you think the important discoveries will come from, who you think will make the important discoveries, and where you want to put your resources. So we no longer have an endocrinology department; we no longer have a cardiovascular department. I have let people go, sometimes people that have worked with the company for a long time--fifteen years. These are painful, sometimes controversial decisions that one needs to make.

Hughes

Did you come knowing that you would do those things?

Scheller

[pause] I thought I would probably do those things but hadn't thought about how stressful they would be to do until I actually began to do them. It's very different than academia. If I had a student that wasn't doing very well, I just wouldn't talk to him all that much, and he would work away for a few years, and he'd eventually go away. But I didn't fire anybody.

Hughes

Is that power in your hands at Genentech?

Scheller

Absolutely.

Hughes

There's no approval process of any kind that you have to go through?

Scheller

No. Again, something that's different than academia. To let someone go at the university would be an incredibly involved process. It would be in many cases impossible. [laughs] Here, if it's in the best interest of the business, it's something that we do.

Hughes

I meant my question to be broader, not about dismissing individuals but about changing program emphasis.

Scheller

Absolutely, totally at my discretion. Not that I necessarily made the decisions in a vacuum. I consulted a large number of people of course. But in the end--my decision.

Hughes

What did you consider when you were reviewing the various existing programs?

Scheller

I thought about the science. I thought about whether the science that was being done would reasonably lead to a medical advance and therefore were studies that we wanted to continue. To be perfectly honest with you, since it involved separations from the company, I don't want to get into the details.

Hughes

I don't want you to; I'm trying to get at your thought process, the conceptual basis, not the specifics of each decision.

Scheller

The kinds of things that I consider and the kinds of things that are publically said don't always 100 percent overlap.

Scheller's Postdoctoral Fellows Follow Him to Genentech

Hughes

Are you doing any research on your own?

Scheller

Sure. I brought with me five postdocs and my research associate of twelve years. I have a lab and we're working away. My hour of sanity every week is my lab meeting where we go over data. We meet in this room. We wouldn't have fit in this room at Stanford but we fit in this room here. I'm not sure that I will keep a lab of that size. These people had nowhere else to go and I had of course a commitment to them. I announced in December that I was leaving in seven weeks. That doesn't give a person a lot of time to change their life. So I was happy to have a number of them move here, and they're actually very happy to be here. Most of them

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were wondering whether they would pursue a career in academia or industry. They say that during one postdoc they got to experience both. And in general I think they'd say that doing the science is very similar here.

Hughes

Did you have to negotiate bringing them?

Scheller

I told people here that my postdocs would move. This ended up being a few more than I actually hoped would move, but as I said they had nowhere else to go. I assumed that they would want to stay at Stanford or leave. I was surprised that almost everybody said, "Oh, no, I'd love to move to Genentech." Then I thought, "Oh, well, I didn't know you were all going to want to move." [laughter] I discouraged a few people from moving.

Hughes

What was the reason? Their respect for you or the fact that they wanted to try working in industry?

Scheller

They were much more open to doing a postdoc and their research in industry than I thought they would be. It gave them confidence that it was an okay thing to do if I was doing it.

Prevailing Stigma against Industry Scientists

Hughes

In general, academics used to consider that a scientist choosing to go into industry probably did so because he/she couldn't cut it in academia.

Scheller

There's still a stigma in academia that that's the case. I think it's a one-way street. Most people in industry don't think that, but that's understandable. Can't say that about me because I've done both.

Hughes

What do your academic colleagues say to you about your transition to industry?

Scheller

I think that some of my younger colleagues probably don't get it, but most of my colleagues that are more my age or older completely understand that I just wanted to do something different because they probably all thought the same thing themselves.

Hughes

Were you doing any bench science at Stanford?

Scheller

No.

Hughes

Do you miss it?

Scheller

I stopped bench science so long ago that I can't even remember. If I tried to pipette I would probably not be able to.

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Genentech's Pharmaceutical Production Capability

Hughes

Part of Genentech's business, of course, is development and scale up. Do those two aspects broaden the way you have to plan the science? Or can you say, "That's the responsibility of other departments; my responsibility is to see that good science is done?"

Scheller

Development is taking the molecule and turning it into a drug. Production is really not something that I work on or think very much about. I am awestruck by what Genentech does in terms of manufacturing. The thought that in my lab we grow a little flask of a couple-of-hundred mils that we shake around and work on, whereas in our production plant we do 12,000-liter fermentations. When we make protein, if we make a milligram it's a lot. Over the course of a year here we make hundreds of kilograms of pure protein. The scale is something that I still can't even fathom, and therefore it's just amazing and remarkable that it gets done. So I respect it immensely and it's science in its own right--engineering really, which I consider science--that requires tremendous technical innovation and creativity, precision, organization, all leading to something that ends up in a bottle that is sold, shipped, in a doctor's office, and helps someone. It's incredible that it ever gets that far.

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Scheller

[The scale-up] is done largely by the process science group. These are not cheap drugs to make. Then you worry about ways for making cost improvements in the manufacturing. It's not the case that every batch works out. You work towards improving your yields so that the fermentations don't get contaminated and you have to throw it all away, or one of the steps doesn't work for some reason and you have to start over. That can cost many millions of dollars. But that's something that Genentech is very, very good at because of its long history of having recombinant products so early on in the history of the industry.

Hughes

The process science people could say, "That's a grand discovery that you've made, Dr. Scheller, but if you only did it in this way it would make our lives much easier. Would you please put it in an aqueous medium," or whatever.

Scheller

Sure. The cost of goods: "If you only did it this way we could actually afford to make it and sell it to people. Since it's that way it is going to be so expensive that nobody's going to want to use this." There's fairly little of that done since we make a set of antibodies or proteins. What we're looking for is a cell line which produces a good amount of the protein. We and process science can usually come up with that. It's an area of research that we do work on: "Gee, if we make a gram per liter; if there is some way we could make two grams per liter, we'd get twice as much for the same amount of money. That would be a great thing for the company in terms of profits." So we do some research into increasing the yields of protein expression.

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Genentech's Research Review Committee

Hughes

I read of the Research Review Committee which apparently you chair. Would you say something about its functions?

Scheller

The research review committee decides on the directions of research for Genentech. So all of the projects are presented to the standing members of the committee and invited reviewers. We then discuss the project with the scientists that have presented. We then ask the presenter to leave, and we have a discussion amongst ourselves, including the invited reviewers. We then ask the invited reviewers to leave, and then the standing members of the committee draw up a set of action items of our recommendations on how the project should continue.

I've asked all of the scientists at Genentech to present a RRC--Research Review Committee--presentation over the course of the first year that I'm here so that I can get to know both the scientists and the work that they're doing in much more detail. Some scientists present a lot of RRC's, and other scientists have been here five or more years and never have presented one. This again is meeting with various levels of enthusiasm. But it's not optional.

The Hoffmann-La Roche Presence at Genentech

Hughes

Is Roche a presence?

Scheller

No. Four times a year for a day and a half. We were supposed to have a meeting last week which of course we didn't go to [because of 9/11]. Once a year in New York, three times in San Francisco. I present research [to Roche] once a year. It was supposed to be last Thursday, the first talk that I've practiced in twenty years, and now I'll never give it because of the tragedy.

Hughes

I'm not asking for the specific content, but is it a status quo report or a projection of what is to come?

Scheller

A review of where we stand and where we're headed.

Hughes

It's intended for information purposes, not for approval?

Scheller

This particular presentation is for information, feedback on whether the ideas are reasonable and so on. There are certainly other presentations that we make to the board for approval: capital expenditures, stock options, acquisitions, and so on, that require their approval.

Scheller's Scientific "Instinct"

Hughes

You have been described in some of the press that announced your arrival as "having an incredible instinct for science." Is there anything more to be said about what goes into that instinct ?

Scheller

It's not that complicated. It consists of two factors: What I would call your inborn or innate ability to think about the world around you. There isn't very much you can do about that; whatever you're born with is what you get. I presume that I have some at least average talent there. Then your experience, which is also something that I suppose is in part innate: How interested you are; how much time you've spent thinking about science, honing your instincts, developing your instincts, refining them. Since I always wanted to be a scientist and have been thinking about science since I was ten years old, I now have thirty-seven years of experience thinking about science and refining my "instincts." So I think that it's the combination of your innate ability and your experience that gives you what people call "instinct."

Scheller's Contributions

Hughes

What do you see as your most significant contribution thus far?

Scheller

To Genentech, or to science, to the world?

Hughes

I'll leave it to you to define.

Scheller

Well, I think the scientific discoveries that I've made are my most significant contributions, and that the contributions of the last decade--understanding how the membrane compartments of cells are organized--is a very fundamental set of contributions to modern biology that have changed the way a lot of people think about cells. That's certainly the set of contributions that I'm proudest of--period.

Thoughts on the Oral History Process

Hughes

Anything you would like to add?

Scheller

No, I think this has been an interesting process and an interesting project. I'm wondering what happens to projects like this, and how you feel about it. You've listened to me and I've talked. We're going to transcribe this. It's going to end up somewhere. I'm wondering what real value this is going to have for mankind. Who's ever going to read this? Who's ever going to know about this? Why do you do this?

Hughes

Now I'm on the spot. Why I do this interview with you is because the university has agreed with Genentech to do it. But long before this agreement I was interviewing scientists associated with the biosciences and biotechnology. The reason that the university is behind a project like this is to create resources for present and future research use.

Maybe a useful way to think about it would be to imagine what we would learn if we were able to have this kind of a discussion with Pasteur or Madame Curie, one that went beyond formal publications, which often are all we have from scientists, particularly nowadays when people don't keep diaries; they don't write letters; their scientific publications in many cases are pretty much it. You lose a lot of "why" context--the reasons that a person's science took the directions it did. You've been describing the many reasons, beyond the intellectual, for your science going the way it did. I for one find that very interesting, and I hope and I think and I know that others do too. Perhaps in a hundred years it will be even more interesting because the external circumstances will be so very different. Science itself may not be fundamentally different since science, put simplistically, is trying to discover more about the world. That presumably will always be its basis. But just think--not only the technological breakthroughs, but maybe even the ends that people have, the reasons that they do science, may be somewhat different. Who knows? But at least we have documentation of what a number of people in the early twenty-first century thought were the reasons they were doing science.

Scheller

Sure, something to compare it to for a hundred years from now. Good.

Hughes

Thank you for your participation.

Further Discussion of Scheller's Graduate Student Years at Caltech

[Interview 3: January 11, 2002] ##

More on the First Cloning of Synthetic DNA

Hughes

At the request of Genentech, we initially omitted discussion of the somatostatin project, which was your first brush with Genentech, because of current litigation with City of Hope. We have recently been given clearance by Genentech's legal department to talk about it and the work on insulin and growth hormone. You weren't involved with the two later projects. So let's return to your graduate student days, which we discussed in the first session.

Before we discuss the somatostatin project, I want to take up a point that Stephen Hall made about Wally Gilbert's visit sometime in early 1976 to Dickerson's lab at Caltech. [6] Stephen Hall, *Invisible Frontiers: The Race to Synthesize Human Gene.* Redmond, WA: Tempus, 1987, pp. 73-74. Do you remember this episode?

Scheller

Yes.

Hughes

Apparently he gave you some advice.

Scheller

Sure. Itakura had synthesized the 21 base pair lac operon DNA. We wanted to clone it. Cloning wasn't very advanced at the time, and the ends of the DNA were blunt ends; they weren't sticky ends. It was known that you could open up a plasmid with a restriction enzyme. EcoR1 was the first one that was widely used. But the way the restriction enzyme worked left an overhanging, single-stranded portion of DNA. So the synthetic DNA was not compatible with the plasmid because it was blunt ended. One needed a way to make it compatible.

We knew that Herb Boyer had an 8 base pair fragment of DNA that corresponded to the EcoR1 restriction enzyme site. So we had the restriction site, and we had the lac operon DNA, and they all had blunt ends, but there was no known way to get them together. So Gilbert--I don't know how--I can't believe that he actually read it--knew that Khorana had published a paper as part of a massive number of papers on synthesizing genes the old way. He demonstrated that RNA ligase--not DNA ligase--catalyzed a blunt-ended joining of DNA fragments or a ligation. So

that's where the idea came from to take the 21 base pair of DNA, to ligate on the 8 base pair EcoR1 restriction enzyme sites, to then cut that with EcoR1, and then the sticky ends of the synthetic DNA would match the sticky ends of the plasmid that could be ligated together. That's what was done, and that was, in fact, the first cloning of synthetic DNA. That was the first example of where chemically synthesized DNA actually functioned in a living cell. Remarkable.

I remember going home that night to a [Passover] seder; it wasn't a religious seder. I didn't even know what a seder was since I was raised as a Christian. But some friends I lived with near Caltech used that as an excuse to have a dinner party and to drink a lot. [laughs] I told everybody that synthetic DNA had been shown to function in a living cell. I could hardly eat. A lot of these people weren't scientists; I'm not sure that it meant very much to them, but it did to me.

Hughes

And that was 1976?

Scheller

I'd have to check; it's so long ago. When did the *Nature* paper on cloning the lac operon come out?

Hughes

I can find it, but I don't know right now. [7] H. L. Heyneker et al., "Synthetic lac Operator DNA is Functional In Vivo," *Nature* 1976, 263:748-752.

Somatostatin: Genentech's First Research Project

Deciding on DNA Synthesis

Hughes

How did you come to be involved in the somatostatin project?

Scheller

[pause] The somatostatin experiment started when I was a graduate student and Itakura was at Caltech, and that really was the only facility in California, maybe in the United States, to synthesize DNA using the triester method that Itakura invented.

Hughes

People like Khorana and Sarah A. Narang were using the diester?

Scheller

Well, Khorana was using diester. That method was much, much slower, and the yields were much lower. The chemistry had to be done in water, and water's not a good place to do chemistry because it's just so reactive. Narang was a student of Khorana's, and he left and started his own lab. Itakura then joined Narang's lab as a postdoc, and he developed the triester method when he was working with Narang, and he brought it to Caltech to work on the lac operon project.

After Herb met Bob and they decided to form Genentech, Herb recognized for a number of reasons that the easiest way to get a gene was to synthesize it. First of all, that got you around the NIH guidelines. Remember, one of the abundant sources of insulin and growth hormone was from tumors. People at the time were worried that if you cloned RNA's and cDNA's from tumors, you might clone something bad, and that something bad would get out into the sewers. It turned out not to be the case, but people were worried about that. I think Herb recognized that you could get around that if you synthesized the gene. There were no cells, for goodness sakes, so how could you get [infected] by mistake?

Choosing Somatostatin as the Molecule to Clone

Scheller

But the synthesis, even though it was a hundred times faster than Khorana could do it, wasn't robust enough to synthesize a real big gene; they had to synthesize a little gene. People thought about what's little but still biologically active. That turns out to be peptide hormones--things like growth hormone, only much smaller. One that was well characterized, meaning it had a physiological activity and there was an antibody available that would recognize it, was somatostatin. [The somatostatin project] was a proof of concept of the whole idea of producing a human protein in a cell. I'm not sure if the idea of the specific hormone came from Art or from Herb. It might have come from Art Riggs.

Hughes

I'm pretty sure it came from Art.

Scheller

Somatostatin was a good one to choose. He could have chosen any number of them.

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Hughes

As you well know, Swanson wanted to go straight to insulin and had to be persuaded that somatostatin was the wiser route.

Scheller

Right, and the difficulty there, of course, was that insulin's larger. There were two chains of insulin that had to come together in order to make the active molecule, not something that bacteria know how to do.

A Failed Attempt at Caltech

Scheller

There was a step that never worked out, which was that we'd put in the first several amino acids of somatostatin and then probably [beta]-galactosidase behind it. I don't know if anyone ever talks about this because it didn't work. It's probably my fault that it didn't work.

Hughes

But that was what you were told to do?

Scheller

Itakura and I synthesized two pieces of DNA and encoded the first few amino acids of somatostatin. We were then going to put [beta]-galactosidase in frame so that we'd make the first few amino acids of somatostatin, then [beta]-galactosidase. We felt that that was enough to show that we could direct the bacteria to make what we wanted. Itakura and I made pieces of DNA at Caltech. I think the one that I was synthesizing was probably particularly tricky, and I wasn't as good at it as Itakura. It had a lot of G [guanosine] and C [cytosine] in it, and the piece I tried to make didn't work out.

Hughes

G's and C's are harder to synthesize?

Scheller

G's in particular. So the piece I was making didn't work out.

Hughes

You mean it had mistakes?

Scheller

Well, it wasn't right for some reason. So, yes. Whether it had mistakes, or it just didn't have something it was supposed to have; or it had something that it shouldn't have, I don't remember.

It was at that time that Itakura was moving to the City of Hope. His labs were done there. He was recruiting in more and more people, so it wasn't just the two of us anymore. It was easier for him to more rapidly synthesize the whole gene, which took several pieces of DNA, not just two pieces, because he had several other chemists coming in.

Hughes

Which he did at City of Hope?

Scheller

Yes, although he started at Caltech.

Hughes

You mean, started on synthesizing the whole gene?

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Scheller

He certainly brought things from Caltech that he used at the City of Hope. How far he got I don't remember.

Hughes

Did you drop out at that point?

Scheller

Yes.

Scheller's Confidence in Bacterial Production of Human Peptides

Scheller

So then I decided, "Of course this will work. All I have to do is put the DNA in there. Of course the bacterium doesn't know what to do [without the DNA code]. It's going to make whatever protein [coded by the DNA] you put in there." That's a no-brainer.

Hughes

Well, I don't know that it was a no-brainer to everybody.

Scheller

Oh sure. How could it not work?! If the whole foundation of molecular biology was wrong it wouldn't work. But that was pretty unlikely.

Hughes

At that point enough was known about *E. coli* as compared to a eukaryotic cell that you wouldn't expect it to reject eukaryotic DNA?

Scheller

There was more known about *E. coli.*

Hughes

Well, I know that.

Scheller

An amino acid's an amino acid, and you knew the genetic code. So what could have gone wrong is that the RNA might not have been stable enough; the *E. coli* might have degraded it. Or the protein that was made might not have been stable enough.

Hughes

Or didn't fold right.

Scheller

But it's a peptide; there is no folding of the peptide. It doesn't have a [three-dimensional] structure. That's also why somatostatin was a good one to try in the first place.

Hughes

Was that actually thought about? Somatostatin doesn't have a three-dimensional structure; this is another reason why we should have somatostatin as our test molecule?

Scheller

I don't remember that ever being discussed. It was mostly just that somatostatin was small. And remember, it was made as a fusion to [beta]-galactosidase, so it was made as part of a bigger protein. Then it was cleaved away from the [beta]-galactosidase by treating with cyanogen bromide, which will cut the protein chain at the position of a methionine. That was done in vitro--that was done outside it when there was no more *E. coli* left.

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Initial Failure

Hughes

Was another consideration that there was a methionine?

Scheller

It was a worry that the protein might not be detected, even though it was made, because it was degraded.

Hughes

That did happen.

Scheller

I don't remember.

Hughes

Well, it happened after you dropped out of the project. Swanson had flown down to City of Hope at a stage where the *E. coli* were supposed to be spitting out somatostatin, and nothing came out. Swanson practically had a heart attack. It was later found later that *E. coli* was chewing up the somatostatin, which was only being produced in a very small amount.

Scheller

Right, but that was why the antibody was originally thought to be useful and that even if the *E. coli* didn't make a lot of somatostatin, even if the *E. coli* made a tiny, tiny amount, that their antibody detection was so sensitive that it would be detected that way. So not like the kilograms that we make nowadays. If billions-fold less was made, you'd still be able to detect it. That would be evidence that even though the process wasn't effective, that at least it was working. The details and the ins and outs of exactly how all that happened and whether it worked exactly the first time, I don't know because I wasn't there.

Hughes

It didn't work the first time. I thought it was at that point that they decided to make a fusion protein which *E. coli* would be less likely to chew up.

Scheller

It might have gone through [three] phases. The first one we were going to make was definitely a fusion protein. Then maybe--I don't remember exactly--it was decided to make just somatostatin. Then maybe that didn't work, and it was decided to make a fusion protein again.

Hughes

I know it was a fusion protein that was in the end successful.

Scheller

That might have been it: fusion protein-straight somatostatin didn't work; partial somatostatin-fusion protein didn't work because of a bad piece of DNA; full-length somatostatin, not fusion protein, didn't work because the protein was degraded; then full-length somatostatin-fusion protein did work.

Caltech had an agreement with Genentech and royalties were worked out. I don't have any records of that. Tom Kiley came to Genentech and negotiated with the technology-transfer people at Genentech--royalties and this, that, and the other thing.

Somatostatin Research to Bolster a Patent

Hughes

Is that enough on somatostatin?

Scheller

Only that it went on and on and on. Somatostatin's still going on. There are still courtroom challenges of the Riggs-Itakura patent. Ten years later Riggs was still doing experiments to isolate somatostatin in a way that was more to support the patent position than to extend the life of the patent. For god's sakes, the science had moved so far beyond that in ten years. There was no scientific reason to isolate somatostatin and show it was pure; it was never going to be a product. Insulin was for sale, on the market; growth hormone was for sale. Why do it with somatostatin? After the initial demonstration, the work moved on for years without any true intellectual contribution. It was only strengthening patent positions.

Hughes

As you know, Riggs-Itakura is a very broad patent. I've heard it described as the corporate counterpart of the Cohen-Boyer patent. So it has implications, I would suggest, that are far broader than its application to somatostatin.

Scheller

Sure, although in the end the money that was made for Genentech and the City of Hope was very significant back then. Compared to [income from] a single product, it's a small amount of money. I never thought I'd be saying hundreds of millions of dollars is a small amount of money. That's the kind of job I have now.

Stock Options for a Graduate Student

Hughes

You got the stock that put you on the front page of the *Los Angeles Times* after Genentech's IPO [initial public offering].

Scheller

I got the famous stock; yes I did.

Hughes

Were you surprised by the stock offer? It's not what the average graduate student of that era would expect.

Scheller

[pause] Well, yeah, sure, I guess. Although Itakura and Riggs had talked about stock.

Hughes

And, of course, they must have gotten some.

Scheller

Some?! They had a huge amount, or what turned into a huge amount.

Hughes

So stock was in the wind.

Scheller

I just took the piece of paper and put it in a drawer somewhere and didn't really think very much about it.

Hughes

You didn't think about it because you suspected the company might not make it? Or did you think, stock is something unfamiliar to me. It is not what most academic scientists of this era are exposed to. They're not usually offered stock for working on an experiment.

Scheller's Confidence in Genentech's Success

Scheller

I had a ponytail halfway down my back. I smoked marijuana every day. I didn't give a damn about money or stock or anything. I was a scientist. I didn't, fortunately, throw it away, but it didn't really mean anything to me. I always thought the company would be successful.

Hughes

Oh, you did?

Scheller

Oh sure.

Hughes

Why?

Scheller

Because it just made sense scientifically. It had to work. I was sure there would be ups and downs. But it had to work. Otherwise, as I said, the whole foundation of molecular biology was wrong. It had to work. I didn't want to do something that had to work. I didn't want to be an engineer. I wanted to discover new things that no one else knew and understand how animal cells work. It clearly was exciting to other people, but if you're a basic scientist that wants to understand the mysteries of nature, making a protein in bacteria is like being an engineer. It's like building a building with a set of instructions rather than discovering what matter is like that the building is built on. So that was my motivation for leaving the project. I wasn't discouraged by failure or anything. It was actually exactly the opposite--I was sure it would work.

Biology Begins to Become Corporate

Biologists with Corporate Ties

Hughes

You don't talk--probably significantly--of any feeling of impropriety for collaborating with the corporate world, which, for a biologist of that era, was not nearly as common as it is nowadays. You were just thinking, I'm interested in basic science questions so of course I will remain in academia?

Scheller

Yes, that's what I always wanted to do. We talked about that months ago. Since I was three feet tall I wanted to be a scientist--not an engineer. I'm not sure it's really different, but in my mind it was different.

Hughes

Do you remember any discussions about Genentech and the controversy that it was causing? One concern was the acceptability of academic biologists making money through a company. Herb Boyer really got it at precisely that time.

Scheller

Sure. There were discussions about it, but I wasn't that much involved in those kinds of discussions. I don't know if my graduate-student peers said anything behind my back, but nobody ever said to me, "This is a bad thesis project. It's not real science." I was well aware of those discussions, but it was not very long after that that Wally Gilbert started a company [Biogen], and X and Y and Z. Boyer might have gotten it, but he got it for only a little while before it was something everybody was doing.

Hughes

One of the sticky points concerned the postdocs who before Genentech had buildings had laboratory space in Herbert Boyer's own laboratory at UCSF.

Scheller

I knew Heyneker and Paco Bolivar [were getting paid by Genentech].

##

Hughes

You were in a somewhat similar position at Caltech. I don't know if you were getting money, but you were getting stock.

Scheller

I was getting money. I was getting an extra check from Genentech every month. It's almost laughable now, but a few hundred dollars. This made me, I would say in quotes, "a rich graduate student." Instead of making $8,000 a year, I probably made $15,000 a year, and I was rich. [laughs]

Hughes

Was this common knowledge?

Scheller

I think that my friends probably knew; I'm sure I told them. But I don't think it was broadly known. I'm not even sure Caltech knew. I don't remember.

Hughes

It did cause problems in the Boyer lab--between those who had a Genentech stipend and those who didn't.

Scheller

Boyer's lab was different than Richard Dickerson's lab where Itakura and I were working. Boyer's lab was a much more active place with lots of students and postdocs. Dickerson's lab was very small, mostly technicians, more senior technicians, and not a lot of students. So it was a much quieter, less competitive environment than Boyer's. I can imagine that it would have caused problems up here.

Jealousy as a Motive for Criticizing Commercialization

Hughes

It was a volatile situation because of the recombinant DNA controversy. UCSF and Stanford were in the news.

Scheller

Sure. I think the chemists and the engineers and some of the physicists were laughing at us. The chemists had been interacting with companies for decades. These crazy biologists just needed to calm down and get this worked out. I think that most of the fervor came from jealousy and that maybe some people even convinced themselves that it was wrong, or not as moral--I wouldn't call it immoral--to be associated with a company. But I think that it was mostly jealousy. Because those people that thought it was wrong and less moral I'm sure are associated with companies; so they either changed their minds, or they didn't really understand their motivation in the first place. I think it's the latter.

Hughes

Times have changed, and the culture now not only doesn't disapprove, but actually encourages technology transfer. The corporate world is looked to as the place to produce products for human health, etc.

Scheller

Sure, but that was always the case. UCSF might have been a little naive in that respect because it's a medical school. Stanford has a chemistry department where the scientists had been working with Merck and Pfizer and so on for decades, and an engineering school where all of the faculty consult, and so on. So I think it was the medical scientists, the biochemical scientists, needing to go through this little period of understanding about how our country works.

Hughes

Stanford from [Frederick E.] Terman days on has been a very entrepreneurial place. But until fairly recently, UCSF has been clinically oriented; it hasn't had industrial ties.

Scheller

I don't understand that completely. Certainly, the physicians consulted heavily with drug companies for more than fifty years and were conducting clinical trials while often being on the payroll of the drug company. I think you've said it right: it was the specific culture of the life scientists that just hadn't been through this before.

I think you don't have the balance quite right. I think there was much more jealousy behind this than real soul-searching and morality. These experiments were so widely talked about, Genentech was so widely discussed, it was clear there was a lot of potential for money involved. It was clearly in the news, on peoples' minds. So it might not even have been Boyer and his money as much as Boyer and all the attention that he was getting: "He's getting all this attention, but he's not really a scientist. He's just doing it for the money." That's jealousy; that's nothing to do with morals. Of course it was more complicated, but maybe not as complicated as you think. [laughter]

Observations on Genentech Culture

Hughes

What were your perceptions of Genentech culture when you first arrived? What kind of adaptions did you make, coming from academia?

Scheller

Well, some of the culture is different and some is the same. I think a lot of the people could get up and walk out of their lab here and walk into a lab at Stanford and sit down and not skip

abeat. They could do at Stanford exactly what they do here and be the same scientist, the same person, the same everything..

They have a little more of a 9-to-5 culture here than at Stanford, but I think that reflects the much larger number of research associates and senior research associates, technicians. There are more technicians per lab and no graduate students. We don't have people young enough to stay up all night. We have a lot of postdocs; they're just a little bit older, and they still stay up all night here and at Stanford. But there aren't as many here, so it's a shift to a non-graduate student, technician-oriented culture. The average age of a person in the labs here is probably some years older. There's a different feel. There are no undergraduates here. Undergraduates are so naive that it's terrific. I love undergraduates. I miss the undergraduate students and the graduate students, and that's the biggest difference, and that reflects itself in a lower level of motivation. The culture's different than in some of the smaller companies. In some of the smaller companies you maybe have to sleep in the lab to get your experiment done, otherwise you're going to run out of money and you're not going to have a job.

Hughes

That's a motivator.

Scheller

You damn well better believe it! [laughter] If you go home here and you do your experiment the next day, instead of staying up all night, you're still going to have a job, because Genentech sells a lot of medicines, so they're not going to run out of money. And that's a difference between the old days of Genentech and now, when people slept here because they weren't sure whether Genentech was going to run out of money.

Hughes

Does personality come into it?

Scheller

Oh sure. And competitiveness and all of those kinds of things.

Encouraging Passion for Science

Scheller

I'm trying to bring the balance back towards that intense passion for science.

Hughes

How do you do that?

Scheller

Well, by the kind of people that you have here--hiring a lot of new people, making sure that those people are the kind of intense scientists that you want. Basically, I think, by just bringing in new people.

Hughes

Why do intense people want to come to Genentech?

Scheller

To do science.

Hughes

But why here? There are many places to do science.

Scheller

[pause] Why here? Well, because of the other people, because of the history, because of the kinds of things we're trying to do. I like to think, in a small part, because of me. Because of some of the other great people that are here.

Larry Lasky, who was a postdoc at Caltech when I was a graduate student, came to Genentech. The first week in January was his twentieth year here. He's resigned. I have of course known him for twenty-five years, whatever. He said to me, "Well, I'm going to leave." I had gotten wind that this might be the case, and I said, "Well, do you want me to try to talk you out of it?" He said, "Richard, don't try and talk me out of it. I'm just doing what you did. You left Stanford to come here for something new and different, to get more excited again about life. I'm doing the exact same thing you did. So then I said, "Well, then there's nothing to say. Good luck." He's going to go to a venture capital firm, so he's trading his blue jeans for a tie. It's those kinds of people that have gone through at Genentech what I went through at Stanford: they've been here so long, it doesn't seem as new and different and exciting as it used to be, just because they've been doing it for twenty years. People like that are leaving. I'm not sure I mind so much that they're leaving. What we'll do is find someone out of a postdoc that's all fired up--that fire in their belly that wants to come in and change the world.

Hughes

There's a paradox, to my mind, about what success means to a company. Some of the attraction to a small company is that you can turn on a dime; it's new; it's exciting. But the price that often comes with success is more corporate structure, more restrictions, more rules, larger size, and, as you're saying, people having been there long enough that it begins to get old.

Scheller

Well, we talk a lot about that in our executive committee--the group of six people that run the company. We talk about what aspects of our culture we can scale to the size that we are now. I think it's Lou Lavigne, the CFO, who said, "What parts of the company are scalable?" That's something that's on our minds all the time because we'd like to keep it the innovative, creative, dynamic place that it has always been. But the point you raise is: Is that possible? It's clearly not possible in every aspect of the company, but it's probably more important to try to keep that in research than anywhere [else].

Hughes

And that's your responsibility.

Scheller

Sure, no problem. [said facetiously] [laughs]

Hughes

You wanted challenges; you've got challenges.

Scheller
I've been here ten months. No problem. Sure. [laughter]

Hughes
Well, you need to get to your beer session. Thank you for your insights.

Transcribed by Jessica Ross Stern
Final Typed by Caroline Bridges

Appendix

Tape Guide--Richard Scheller

Interview 1: August 16, 2001

Interview 1: August 16, 2001
- Tape 1, Side A *
- Tape 1, Side B *
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Interview 2: September 21, 2001
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Index--Richard Scheller

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Graduated from the University of California, Berkeley, in 1963 with an A.B. degree in zoology, and from the University of California, San Francisco, in 1966 with an M.A. degree in anatomy. She received a Ph.D. degree in the history of science and medicine from the Royal Postgraduate Medical School, University of London, in 1972.

Postgraduate research histologist, the Cardiovascular Research Institute, University of California, San Francisco, 1966-1969; science historian for the History of Science and Technology Program, The Bancroft Library, 1978-1980.

Presently research historian and principal editor on medical and scientific topics for the Regional Oral History Office, University of California, Berkeley. Author of *The Virus: A History of the Concept,* Sally Smith Hughes is currently interviewing and writing in the fields of AIDS and molecular biology/biotechnology.
