Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Program in the History of the Biological Sciences and Biotechnology

Laurence Lasky, Ph.D.

VACCINE AND ADHESION MOLECULE RESEARCH AT GENENTECH

Interviews Conducted by
Sally Smith Hughes, Ph.D.
in 2003

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:

> Laurence Lasky, Ph.D., "Vaccine and Adhesion Molecule Reasearch at Genentech," an oral history conducted in 2003 by Sally Smith Hughes, Ph.D., Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2005.

Copy no. _____

Laurence Lasky

TABLE OF CONTENTS—Laurence Lasky

BIOTECHNOLOGY SERIES HISTORY

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] 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

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

March 2005

ORAL HISTORIES ON BIOTECHNOLOGY

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

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

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

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

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

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

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

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

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

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

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

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

Diane Pennica, Ph.D., *t-PA and Other Research Contributions at Genentech*, 2003

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

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

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

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

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

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

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

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

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

Oral histories in process:

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

INTERVIEW HISTORY—Laurence Lasky

In twenty years at Genentech, Laurence Lasky made his mark through front-line research on herpes and AIDS vaccines and adhesion molecules. His first taste of commercial biotechnology came as one of the first scientists at Genetics Institute, a Massachusetts-based start-up with a southern California laboratory. Deciding that Genentech was where biotechnology was really happening, Lasky left Genetics Institute at the end of 1981. By January 4, 1982, he was ensconced at Genentech as a scientist in the vaccine division under Dennis Kleid.

In the oral history, he describes his perception of many of the early scientists, finding deficiencies in some and heaping praise on others, particularly the wunderkind Dave Goeddel. Despite Genentech management's aversion to the vaccine business, Lasky persisted in his research on a vaccine against herpes, eventually developing a successful product which the company sold to a pharmaceutical company. He and his colleagues then turned to research on an AIDS vaccine, an all but intractable problem which proved after several years to be exactly that. Lasky nonetheless had a soaring moment at an AIDS conference in which he garnered exhilarating attention as the lead inventor of what they hoped would be a viable vaccine candidate. "I gave this talk," he says in the interviews, and basically people went ballistic." But it was not to be, and Genentech some years later spun off its AIDS vaccine effort into a company called VaxGen. Lasky also describes in detail his last major research project at Genentech, on selectins, molecules active in blood clotting, inflammation, and other biological processes. He concludes by narrating his move into venture capital, a path more and more biomedical scientists take, deciding to exercise their scientific knowledge in the pursuit of new and hopefully money-making technology.

Two interviews were conducted in June and July 2003 in Lasky's new quarters at Latterell Venture Partners, situated in a high-rise at San Francisco's Embarcadero Center. Open and direct in manner, he was equally so in the interview process. The text makes clear his energetic, unrestrained, sometimes irreverently frank conversational style. Yet the science that so preoccupied him at Genentech shines through, embellished by the telling of the human incidents and reactions that so often are lacking in more formal scientific accounts. Through these interviews, the reader will gain among other things an idea of the idiosyncratic manner in which early research at Genentech was pursued as well as a picture of the company's free-wheeling culture.

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

Sally Smith Hughes, Ph.D.
Historian of Science
Regional Oral History Office
The Bancroft Library
University of California, Berkeley

April 2005

INTERVIEW 1: JUNE 20, 2003
[Tape 1, Side A]

Hughes: Please start with your grandparents on both sides and tell me where they came from and what they did.

Lasky: On my mother's side, both grandparents came from Budapest, Hungary. They were Jews, and like many Jews they left at the turn of the century—my grandfather, Joseph Klein, actually fought in World War I. I have a picture of him in his World War I uniform, and then he left right after that. Most Jews that left became tailors, so he was a tailor. And same on the other side. They were in Kiev, Russia. They left before the Russian revolution because my father, Irving, was born in 1915, and he was born here.

Hughes: Why tailoring?

Lasky: I think because it was something they learned in the old country, and it was easy to transfer here. They could carry everything they needed. I'm not sure why, but certainly it was very common for Jews to be tailors. I even worked in my grandfather's tailor shop when I was a little kid. But only on my mother's side did I know them well. My father's parents died when I was pretty young so—they both had strokes.

Hughes: Where were they living?

Lasky: Well, one set ended up in St. Louis and one set, my mother's side, ended up in Chicago. And then they all migrated to California, to Los Angeles. I'm not sure why. Maybe because of weather, opportunity, things like that. But they ended up in Los Angeles. My father was born in St. Louis, and my mother was born in Chicago. But then I think in the twenties or thirties, well, for my father it was the twenties, for my mother probably the thirties, they moved to Los Angeles.

Hughes: And what did your father and mother do?

Lasky: My father, like a lot of scientists' fathers, was a physician, but what he really wanted to do was to be a professor. He wanted to be a scientist. But he wasn't a real risk-taking kind of person, and so he felt like practicing medicine was a much surer and easier thing than being a scientist, which is true. [laughter] He was an internist for years and years in Los Angeles and in Beverly Hills and had a lot of movie stars for patients. He also was an adjunct professor at UCLA [University of California, Los Angeles], and he either had a lab or he had access to a lab because he did lots of experiments. He was very interested in seat belts and automobile safety, and he was especially interested in people, when they came to a sudden stop, their chest hit the steering wheel. Either he discovered it or he was one of the people who discovered it. But what actually happened then is the heart kept going and the heart banged up against the sternum and actually damaged the heart. So, he wrote some papers on this and actually has a little bibliography, not that many papers. But he always liked to write a lot so he actually wrote other things later on in life, a little biography. He was a very high Mason so he wrote these little stories for the Mason magazine. He loved to write, which is interesting because so do I and so does my daughter Olivia. All three of us are really big writers. So, that is his story.

My mother Gloria was the typical fifties housewife, sixties housewife, but then decided she needed more independence. She graduated from UCLA. Oh, by the way, my father graduated from USC [University of Southern California] Medical School, way back in the thirties, which was saying a lot because Jews actually had a lot of trouble getting into medical school in those days.

Hughes: Yes, I was wondering about that.

Lasky: Yes, it was very tough.

Hughes: So he must have been a very good student.

Lasky: Yes, he was a very smart guy, very good student. And he was a good doctor, apparently.

Hughes: Was there any discrimination once he got in?

Lasky: I never heard about any. I don't think there was too much discrimination, but getting in was difficult.

So my mother went to UCLA and much later in life decided she wanted to get a teaching credential and then became a teacher. My father died about five years ago. My mother is still alive, teaches part-time, substitute teaching.

Hughes: Did your father's interest in science have an influence on you?

Lasky: Oh yes, huge. I remember being interested in science as a very, very small kid. All the books I wanted to read were doctor books or kids' doctor books or little illustrated books of the human body. Even as a small kid, I always was very interested, and having him there made it much easier. You could talk about things, and he would tell me things about how the human body worked. Of course, everything was pretty primitive back then but—that was a big plus having him there. I remember doing experiments when I was a little kid—I had a microscope—and going to ponds and getting things and looking at them under the microscope. So, even when I was very small, I was really into it.

Hughes: Do you have brothers and sisters?

Lasky: Yes, two brothers, but they took very different routes. My older brother Brian is a very smart guy but sort of had mental problems and drug problems, lots of problems. He ended up a school teacher although he was very close to getting a Ph.D. in parasitology. He is my stepbrother, and he was shuttled between different families. He had kind of a rough childhood. Now he's retired, living in Humboldt County.

Hughes: That sounds all right.

Lasky: It sounds like we don't know too much what he's doing.

Then my younger brother Marc also wasn't much of a student and never finished college but was incredibly mechanical, always interested in cars and all this stuff. He ended up being a very successful auto shop owner, mechanic sort of repair person, and

he's got this gigantic mechanic shop in Los Angeles. He repairs all these super expensive cars, and he builds cars. He loves that.

Hughes: It sounds as though the pressure might have been on you in terms of intellectual achievement.

Lasky: Well, I was always interested in intellectual stuff so I never felt pressured. I always put all the pressure on myself. So no, I never felt that. My father definitely thought I was going to be a doctor. He really wanted me to be a physician. But when I was in UCLA as an undergraduate, I didn't think being a doctor was going to be interesting enough. It seemed too much rote stuff.

Hughes: Did you start out as a pre-med student?

Lasky: Yes, I had lots of majors. [laughter] You want to move from the family to my education?

Hughes: I skipped you ahead to college. Let's go back a little bit.

Lasky: Well, so the other thing I did as a kid was music, lots of music. My father was a musician, too, and the more I think about it, the more I'm like my father. [laughter] I'm sure you've heard this before. So, he was a musician. Again, though, he didn't ever really go far. He wasn't the kind of guy who pushed himself to do things, kind of afraid of failure or whatever his reason was. But we always had music in our house, and it was always classical music.

Hughes: What was his instrument?

Lasky: He played organ, piano, and percussion, but mostly organ and piano. And he would play organ all over the place, wherever there was an organ he'd play it.

Hughes: Well?

Lasky: Yes, he was a fairly good musician. He never practiced, but he could have been very good. We had a piano, a really good piano, in our house, a Steinway B, and we also had an organ in our house. He would play it after dinner. My mother wasn't crazy about it, but I thought it was great. He exposed me to music very early. Until I was really late in college, I really couldn't decide whether I wanted to be a musician or a scientist. It ended up causing a lot of problems.

Hughes: We'll touch on that in a minute. What instrument did you play?

Lasky: Well, I took piano like every little kid, but it was too hard. I wanted to be a drummer, so my father said, "That's great." I started when I was about nine or ten, taking drum lessons and ended up taking lessons for years and years and playing all the different percussion instruments. It was always classical, though I was in a rock 'n' roll band for a few years because it was fun. I always ended up being in orchestras. I was in lots of different orchestras. When I was still in high school, I played in the Los Angeles Philharmonic. In fact, I played with them several times. I played tympany, that was my favorite instrument. My teacher was the head percussionist of the Los Angeles

Philharmonic, and when they needed an extra drummer to play triangle or cymbals or you name it, I would go and do it. So, that was incredibly thrilling for a little kid.

Hughes: Yes, I bet.

Lasky: First of all, they paid me to do it. I couldn't believe it. I got like a hundred dollars to play and that was great. I owned a tuxedo and tails and all this stuff. My father was very proud of me.

Hughes: What did your friends think about that?

Lasky: They weren't into music so much so they couldn't really understand it. But even throughout college, I was doing lots of music like that. So, it did cause problems because I wanted to be a scientist. But I also thought maybe I wanted to be a percussionist because it was a lot of fun. But it's hard to be a percussionist because there are only a few good orchestras. I went to a music conservatory for a while, the Manhattan School of Music [1971]. I was a double major throughout most of UCLA [1969-1973].

Hughes: Did you drop out of UCLA for a while?

Lasky: Yes, I left UCLA for a few months. I had a girlfriend who was a ballerina in the New York City Ballet, so that was one reason I wanted to be in New York. And two, I wanted to go to Juilliard, but I didn't get in. But I got into Manhattan, which is a very good conservatory. So I thought I should try this and see if I could make it as a musician. What happened was, as soon as I got into New York, I said I'm not going to be able to get into this; this is too cutthroat. There are too many good players. I just freaked out basically and decided, nah. But it was good because it sort of induced a choice that I had to make.

Hughes: The competition was amongst the music students?

Lasky: This was New York. It's the greatest place in America. The players were incredible. The pressure was huge. In science there is a lot of competition, too, but there's so many different fields to play around in. You can always find something that you can be good at. In music there are, say, twenty great orchestras, and each one has four, five percussionists. That's it. There are like eighty jobs out there. And the percussionists are there for life. I mean, they never retire, these guys. I probably could have made it, but in hindsight, I have no regrets about not doing music because I still do music. I still play in orchestras. I still love music, probably as much if not more than science.

Hughes: Well, it's easier to do music on the side than do science on the side. [laughter]

Lasky: Exactly. I sort of miss being at the high end of music. I'm an amateur. I'm in the UCSF symphony orchestra, but it's really bad, but it's fun. We rehearse, and we have concerts. Music's always been hugely important to me. And my kids now are, especially my older one, she's obsessed with music.

Hughes: Was it a given that you were going to go to UCLA?

Lasky: Well, no. My parents were very worried about me. I tend to push my kids too much. They didn't push us enough. All my pushing was endogenous. My father was a USC graduate so he said, "You're going to USC." So I said, "I don't want to go to USC." But I had to go to USC for a semester and hated it. Then they let me go to UCLA. I'm not sure why I didn't even think about going to another university. My grades were good and all that but I guess I just wasn't ready to leave or something. UCLA back then was kind of good but not like now. Now it's one of the best universities in the country. But scientifically it was good and had good pre-med. It was the seventies and you probably remember nobody knew what the hell was going on at the time. You know, the draft, and we were all worried about going to Vietnam. So a lot of it was just getting somewhere, and once I was there I actually liked it. I didn't like the curriculum so much, but the place was beautiful. There were a lot of beautiful girls, and it was a fun place to go.

Hughes: Were you living at home?

Lasky: No, I lived in the dorms, and then when I was in graduate school [1973-1978], I looked for an apartment.

Hughes: So you went right on to graduate school.

Lasky: Now, why that happened was—I wasn't sure what I was going to do. I was half the time music major and half the time biology major. I think I was *cum laude* or something. It was good but not like [I was] going to get into MIT grad school or Caltech or something. And I wasn't really sure about graduate school. I was interested in parasitology. I thought that was really interesting. Those days were early molecular biology days, and right at the end I took a class which was called molecular biology.

Hughes: Now, this was as an undergraduate?

Lasky: This was as an undergraduate. It was taught by this wacky guy named Winston Salser, and it was the most exciting thing I'd ever seen. I just thought it was the greatest stuff I'd ever heard.

Hughes: So, that would have been 1972, 1973?

Lasky: Yes, '73. The genetic code had just been broken, and people didn't really know anything about anything. It was just the early days, but it was so exciting. And I just thought it was the greatest thing on earth; I instantly liked molecular biology. I don't know why I liked it so much, but I just had this instant like excitement and rapport with it.

Hughes: Had your courses up until then been holistic biology?

Lasky: Yes, the more traditional physiology, which was incredibly boring. They stick electrodes in cockroaches, that kind of stuff. It was horrible. In those days, real biology was so physiological. It wasn't molecular at all. But what I think I liked about molecular biology was the fact that, without actually seeing anything, you could make these incredible conclusions, just by being clever, and I thought that was amazing. With physiology, you squirt some compound into a rat, it would do something. Whereas with molecular biology, you had to be clever and then you had to interpret the data. But you

never actually saw what was going on with your own eyes, and that I thought was really phenomenal.

Hughes: Was there a lab connected with the course?

Lasky: No, because there wasn't a lot you could do in those days. Now a kid could go into a lab, and he could cut DNA, and he could clone it, and he could do sequencing. In those days, it was mostly genetics. And a lot of the conclusions that were reached, like the fact that the genetic code was a triplet and that DNA replicated a certain way, was done by genetics or by very simple-minded experiments. It was unsophisticated but clever, extremely clever stuff.

Hughes: Yes, and I gather that Salser was a great teacher?

Lasky: He was incredible. He ended up very badly; he kind of went crazy. But he was an incredible teacher. It was supposed to be like the hardest class you could take. I had taken chemistry, and I didn't do well in chemistry because I thought chemistry was incredibly boring. I mean, who cares about all these organic reactions; I just wasn't interested at all. Molecular biology was supposed to be an incredibly hard class, but I just aced it. I got like one of the highest grades. I was always one of these people that if I liked something, it would just zoom right into me, and I would just know it. But, if I didn't like something, I just couldn't care less. [laughter]

Hughes: Because you were doing so well and so interested, did you have any particular relationship with Salser?

Lasky: No, the class was easily hundreds of kids, and he was an aloof guy. The TA [teaching assistant] was a geneticist, and I had a relationship with him. He was a very nice guy. In fact, on the final exam, which was a huge final exam, he was a proctor, and he walked up to me in the final and said, "Let me see your test." He thumbed through and he said, "You're screwed," and he walked away. [laughter]

There was no lab. It was so early that there really wasn't much you could do yourself. You could only read about it and think about it.

Hughes: Was there a text? There was Watson's book by then.

Lasky: Yes, it was Watson's book, *Molecular Biology of the Gene*.

Hughes: I think it came out in the late sixties.

Lasky: Yes, it did. That was the original compilation of everything that was known from how DNA replicates to the genetic code to ribosomes and all sorts of early stuff. I don't even remember studying hard for the course. I liked it so much that I understood it instantly.

Hughes: Was pursuing molecular biology your motivation for graduate school or what?

Lasky: Well, that was more complicated because, again, there wasn't a lot of molecular biology you could do back then. The experiments people were trying—there was no cloning yet, remember?

Hughes: Yes.

Lasky: They were trying to isolate genes but that wasn't working very well. I started out in a parasitology lab. People would try to translate proteins in test tubes and see what proteins were made and stuff like that. The guy I worked for was named Larry Simpson. He's a really smart guy but a terrible mentor. I mean, he was just totally affect-less, robotic kind of guy. I worked in that lab for a year. Nothing happened, and then there was this other guy in the lab who had worked for four years and had zero data. So I thought, "You know, I better get out of here." [laughter]

So, then I wanted to do something molecular, and the kind of stuff people were doing were hybridization experiments; it was actually clever stuff. It was a kinetic kind of argument: the more complicated a mixture of genes is in your test tube, the longer it takes for the two strands to come together. So, by looking at how long it takes for mixtures of strands of RNA or DNA to come together, you could then, by simple mathematics, deduce how complicated a mixture was in there. That was the sort of stuff people were doing. People were trying to figure out how many different genes were expressed in a certain cell type.

There was a guy there, Allan Tobin, who was the opposite of Larry. He was an emotional, Jewish guy who was from Harvard, didn't get tenure, now with UCLA. He was not a very good scientist, really smart guy, really nice guy, but he was too wild. His brain was not focused. He was kind of all over the place. But the great thing about him for me was, he had a good system which was red blood cell development, which people liked back then because it was so simple. Red blood cells have just a few genes so you could actually do these kinds of experiments. And the great thing about Allan is he left me alone, totally. My whole thesis I did totally by myself, which was a great training ground. I figured out how to make the radioactive nucleic acid and how to do the hybridization and everything. That was good because I learned how to do science on my own and be self-reliant. Allan was the perfect; he wasn't a control freak at all. He was the opposite, which is actually pretty unusual in science.

Hughes: Were you talking to him about your work?

Lasky: Oh yes. We'd go over data, and he would kind of suggest experiments, but it was really straightforward what to do. And I knew what to do. There was another guy in the department named Bob Goldberg who was doing the exact same experiments as I was doing but in plants. And Goldberg was a lot more like me. He was this super-rigorous, anal scientific guy. Allan's lab bench looked like a disaster area. And my lab bench was always like immaculate. Everything was perfect, in its place. All the pipettes were cleaned. So, Bob and I got along much better from the technical standpoint than Allan and I did.

Hughes: Was this the Department of Molecular Biology?

Lasky: It was called then the Department of Biology. UCLA ended up having a molecular biology department but much later.

Hughes: Well, it tells you something, doesn't it?

Lasky: Oh yes; it was very early. I remember people talking about cloning like, "Did you see this paper in *PNAS* [*Proceedings of the National Academy of Sciences*]?"

Hughes: Well, I was going to ask you about that because that first paper by [Stanley N.] Cohen and [Herbert W.] Boyer comes out in 1973, the year you graduated.

Lasky: Right. People couldn't quite figure out what it was good for, and what you were going to use it for. And what is a plasmid? Nobody knew, unless you were a bacterial person. I didn't know what restriction enzymes were, I didn't know what plasmids were. I was doing the same experiments in red blood cells that everybody else was doing and gut and heart. Everybody was doing these same kinetic experiments back then. That was a standard, early molecular biology experiment to do.

Hughes: It's an interesting point though, isn't it? Now, high school students are cloning and all of that. But, it wasn't obvious in the early seventies, was it, that recombinant DNA was going to be almost universally applicable?

Lasky: No, absolutely no. It didn't even get in a good journal. It was in *PNAS*, a so-so journal. And, who's this Herb Boyer guy and who's Stan Cohen? These were bacterial geneticist guys. Stan Cohen worked on plasmids, and Herb worked on restriction enzymes, R1.

Hughes: Would *PNAS* be a journal that people would have kept track of?

Lasky: The hot journal back then, as now, was *Cell*. People would have read *PNAS*, no doubt about it. That was a journal that everybody read. Why did it get in there? I'm not sure why it was in there. The other hot journal at that time was *Journal of Molecular Biology*. This paper was sort of so out there; I think the editors or reviewers just didn't get it. I know Herb Boyer; I could ask him. It would be interesting to know the history of it. But I think most people just didn't get it. It was so very different from what everybody else was thinking about then.

Hughes: And if you read that paper, you can read between the lines now, knowing what we know. But it was not crystal clear at the time what you could actually do with this technique.

Lasky: Not at all. And I don't think it was actually that clear to them. They were holding back. And there were other people, like Paul Berg and [Dale] Kaiser, who were thinking about putting pieces of DNA together. In fact, Berg won the Nobel Prize for that for some reason, which nobody still understands. So people were thinking of sticking pieces of DNA together. They were going to put it in viruses and all this stuff. In fact, it turns out that the original idea of putting it in plasmids is the way it's still done. People do viruses, but most of cloning is done in plasmids. So, that original way of doing it was in fact extremely ahead of its time.

Hughes: It's still done in plasmids because they are easier to work with?

Lasky: Easy to manipulate and they're small. They have antibiotic resistance markers; they have lots of restriction sites. It's just the way it's still done.

Hughes: And of course Cohen's interest was in antibiotic resistance.

Lasky: Exactly. But can you imagine, they had this idea that must have been amazing when you think about it.

Hughes: Well, it was a meeting of the minds. That's for sure. [laughter]

Lasky: Earth-shattering. I think it's the technically greatest discovery of that second half of the twentieth century.

Hughes: Do you?

Lasky: For biology, for sure. Nothing else could have been done without it. And why they didn't win the Nobel Prize, it's just—

Hughes: Well, we should talk about why it was Berg.

[Tape 1, Side B]

Lasky: —really completed the experiment that he thought was too dangerous because he was using a tumor virus, SV40. My personal feeling is it's because Herb—who I like a lot; he's a great guy—was very irreverent and made a hell of a lot of money off of cloning, hundreds of millions.

Hughes: Through Genentech, you mean.

Lasky: Yes, and, you know, he deserved it. Why not capitalize on the great discovery? And I think that was a big part of why he failed to get the Nobel Prize. I don't think it's a good reason, but I think, unfortunately, that was a big part of it. And once they gave it to Berg, I guess, for the idea of binding pieces of DNA together, bacterial and non-bacterial, then they said, "Well, we can't give it to Cohen and Boyer."

Hughes: The Nobel can go to three people. Why not Berg, Cohen, and Boyer?

Lasky: Well, the worst off of all is Cohen, who got a lot of money out of the Stanford license. But he didn't get tons of money or the Nobel Prize. I've had dinner with him a few times. My brief experience with Stan is that he's quite bitter about that. He's not a happy guy, because he thinks he deserves it, and I agree with him 100 percent.

Hughes: But Cohen was in a position similar to Boyer's, and he could have leapt into commercialization.

Lasky: Yes, but he didn't. He never did. They couldn't give it to Cohen without Boyer. It had to be the two. Now, does Herb care? Yes, I'm sure he cares. But you know, he's going around in a Jag[uar]; he's fishing; he's retired; he's giving buildings to Yale. He's having a good time. He was always the kind of guy who knew how to have fun. He's a really—have you talked to him yet?

Hughes: Yes, I have.[1]

---

1. See the oral history in this series with Herbert W. Boyer.

Lasky: He's a great guy. He's just a really great person.

Hughes: Well, they're very different personalities.

Lasky: Cohen and Boyer?

Hughes: Yes, Cohen and Boyer. That's polar.

Lasky: Yes, oh totally. No, Stan is like this. He's still publishing all these papers. He's got an active lab.

Hughes: Yes, their lives took different turns, didn't they?

Lasky: Yes, but certainly two of the great scientists of the century. No doubt about it.

Hughes: When did you finish graduate school?

Lasky: Seventy-eight.

Hughes: Recombinant DNA must have been penetrating academia.

Lasky: So then we can go into my postdoc [1978-1981] because that is a big change. So it started to sink in to everybody that cloning was going to be phenomenally powerful for isolating any gene you wanted to get out and study. But it was still very early and lots of people couldn't do it. It wasn't like now where you can call somebody and get a kit. It was very hard to do. The restriction enzymes stunk; the quality was bad.

Hughes: Were they commercially available?

Lasky: Very few, maybe a couple.

Hughes: So then you had to borrow them?

Lasky: You had to make them yourself.

Hughes: Oh, you made them?

Lasky: Run the columns if you wanted a certain restriction enzyme. At Genentech at the beginning, people were making their own restriction enzyme. Herb Heyneker, I think, made the restriction enzyme.

I was working on this hybridization stuff but I wanted to learn cloning, and I also wanted to stick around LA because I had a different girlfriend [laughter] so I didn't want to leave LA. I thought Caltech was great. And there was this guy, Eric Davidson, at Caltech who was a potential Nobel Laureate, super giant scientist guy. I think I was trying to get into his lab. At that point he was one of the most famous gene regulation people. He and Roy Britten had come up with a theory of gene regulation called the Britten and Davidson model which suggested that genes that all turn on at the same time must have regulatory regions upstream or around that are very similar. Before that time, people had noticed there were repeated sequences in DNA when they did these

hybridization experiments. So, Britten and Davidson reasoned that the repeated sequences are probably these regulatory regions and that turning on genes is a simple matter of protein binding to an appropriate subset of these repeated sequences to turn on all the genes to make hair or legs or an eye or whatever. He was at Caltech, which was an awesome place. I applied and he took me. I was kind of shocked. [laughter] But he took me.

Hughes: Why do you think he did?

Lasky: Well, because I had three papers and they were in very good journals. But I don't know. He saw something.

Hughes: Did you go talk to him?

Lasky: No. I just sent him my proposal and CV and some letters. That was it.

Hughes: And the proposal was right on to what he was interested in?

Lasky: Well, I can't remember. Actually, the proposal might have been something he and I wrote afterwards to get my funding. I think I just sent him my CV and some letters of recommendation. So, I was kind of shocked but I was happy because that was really my ticket to the big time, being at Caltech, although I didn't know that at the time. First of all, I had never been to Caltech. But it ain't UCLA. For example, it's got three hundred undergraduate students, total. Second of all, it's got like a gazillion Nobel Prize winners. [Richard] Feynman was there, [Murray] Gell-Mann was there, Max Delbruck—I saw him every day. This was an unbelievable place for science. It's this little tiny campus out in Pasadena. It was just an amazing place. So, I get into this lab. The lab is huge. It's full of all these unbelievably smart people—I'm not used to this, right? I'm like this little punk, but what's happened throughout my career is I've always managed to claw my way to the same level as my peers by hook or crook. I didn't do that well at Caltech for various reasons. So there's all these guys, and they're all maniacs, and they're all like top of their class. And Eric is this unbelievable control freak. I don't know if you've ever met or seen this guy.

Hughes: No.

Lasky: He dresses like a cowboy. He rides a motorcycle. He's totally macho. He's the only National Academy member to ever have played NCAA football at the same time. Caltech has club football and he was on their club football team. Smokes cigars in his office, drank whiskey in his office. Had math lessons every week. Had a math tutor because he thought for sure that deep understanding of mathematics would solve the mysteries of developmental biology.

Hughes: Now, make a link there.

Lasky: He just felt like quantitative biology was the answer to everything.

Hughes: Was that a Delbruck influence?

Lasky: No. That was more a Britten influence, I think. Roy was a physicist, really. I'm not sure about the dynamic between Britten and Davidson, but I think there was a lot of jealousy on Eric's part because Roy was this very aloof guy who came up with this brilliant idea about how to look at kinetics of hybridization of DNA and that drove Eric to do lots of other things. Eric himself is an incredibly smart person—brilliant, phenomenally brilliant. The two of them were just amazing. The other neighbors: Lee Hood was next door. Tom Maniatis was upstairs. This place was just hotter than hell. It was probably the best place to do molecular biology in the country, especially for cloning. So, I got myself into this thing and you know, Eric would kind of say, "What do you want to do?" And I said, "I don't know. What should I do?" He said, "Well, you decide something to do," which I actually liked in the long run. He became more in control after you decided what you were going to do. So what I decided to do, which in hindsight, if I patented it, it would have been incredibly good. But I didn't.

You know these DNA arrays? Well, I decided to do that in 1978. I wanted to take collections of cDNAs—cDNAs are copies of genes—and I wanted to put them in microtiter wells just like they do now. And then I wanted to stamp them on filters and look at hundreds of genes changing their expression throughout development. And the developmental system Eric used was the sea urchin. It was perfect. We had this animal that developed in the lab, and we could isolate RNA from it. Then I could label the RNA and then add to these filters and look at genes going up and down. It's the exact idea of arrays—exact.

Hughes: Now, where had you gotten the idea?

Lasky: I just thought to do it. I don't know. Later on, I did that a lot of times. I got an idea but instead of worrying about it, I would just do it. And there were other cases later when that happened.

Hughes: And Davidson was open to something that seemed a little wild?

Lasky: Yes, he wanted cDNA libraries, and he thought, well, at least I get out of this some cDNA libraries. The technical challenges were pretty enormous. It was hard to make big cDNA libraries.

Hughes: Why was that?

Lasky: The enzymes were bad, the RNA would get degraded. So it was hard to get high cloning efficiency. All kinds of reasons. And I was very iconoclastic in the lab because nobody else was making cDNA libraries but me. So I was also ahead on that. Actually, very few people were making cDNA libraries randomly. Most people want the hemoglobin cDNA or the active cDNA. I didn't care; I just wanted all of them. Afterwards, when I saw one having an interesting pattern, I was going to sequence the gene and say, "Well, this gene X does all these things." So I went through all this, got no help from anybody, had to figure it out all by myself, and in the final analysis we did publish a paper on it. By that point, Eric and I were not getting along. [laughter] Let's put it that way.

Hughes: Now is this the first paper?

Lasky: No, it's a *PNAS* paper. I think it's 1980.

Hughes: Yes, 1980.

Lasky: So, why weren't we getting along? Well, first of all he was trying to control me, and I had to go in there one-on-one with him. I was intimidated by him because he's a big guy. It just started to wear on me. And the lab wasn't very nurturing, and it was very high pressure. We had these things that were called info sessions, and everybody in the lab would sit in his office. He would just nail people. It was actually good, in hindsight. Getting smashed in the most rigorous manner really is how science works the best. But it was hard.

Hughes: Yes, you were not very old at that point.

Lasky: I was not getting along with Eric so hot. A really good friend of mine, Richard Lawn, is upstairs in [Tom] Maniatis's lab. And Maniatis is very different from Eric Davidson. First of all, Maniatis is a very controlled, unemotional guy, and he is the most hard-working human being I've ever seen. He is there when I walk in and then when I leave he's there, and when I come back at night he's there. One o'clock every night he's there, just working like a maniac. He's totally obsessed with science.

Hughes: Now, he hadn't been at Caltech long.

Lasky: No, he was at Harvard. Then they lured him there to Caltech. Basically, he was figuring out how to make a library out of human DNA, the human genomic library.

Hughes: That's pretty interesting, too.

Lasky: This is huge. This is what this guy is trying to do. At the same time, he's trying to figure out hemoglobin and how the genes of hemoglobin look, and he's trying to figure out the mutations in thalassemia by sequencing the hemoglobin genes. Remember, alpha or beta globin was the first gene that was sequenced. Tom did it. This guy was a big-time molecular biologist. He was amazing. Lawn is my best buddy. We ran marathons together. We're always talking and always excited. Dick is like this. He's still my best friend twenty years later. So, he's in Tom's lab, and they're doing this stuff differently up there, and I'm kind of interested in Tom. But because I'm so pissed off with Eric, I'm like ready to leave. So I was there for two years, and I made these libraries and I've done this stuff. I could have done lots of things, like taken these genes and figured out what they were doing and all kinds of things.

Hughes: But you hadn't gotten beyond the libraries?

Lasky: No, we did the libraries, we did the screening, we showed a bunch of genes changing. And then I was thinking, I just can't handle this guy anymore.

Hughes: It was the control thing that was getting to you?

Lasky: Control and kind of wanting to go out on my own. Now, that was happening plus biotech was beginning. So, first of all, what is biotech? This is 1980. There is one company, Cetus—some of my friends were there. Nobody knew what was going on there. Then there's Genentech. There are a couple more starting to form, like Biogen and Amgen. That's pretty much it, though. It was like four or five biotechs. What is

biotech? So, I started looking into this stuff. Lawn was a hot property because Lawn had all these great papers on hemoglobin, and he was a very good molecular biologist and a very smart guy. And Genentech had hired Lawn. So, we're out doing our runs, and who is Genentech? He said, "Oh, it's an incredible place. They're going to change the world. They're going to make proteins out of insulin genes and growth hormones and all kinds of stuff." And I'm thinking, wow, that sounds really cool. You can actually do this stuff? And he said, "This guy Goeddel, he's so smart," and he's just like beside himself with excitement, right? So I think, God, maybe I want to go into one of these biotech places because I'm not going to get a good enough academic job because I didn't do enough as a postdoc. Maybe I'll even have to do another postdoc, and I don't know if I want to do that.

So then I go up and start talking to Tom, and Tom had started a company. Tom knew I could make cDNA libraries. Believe it or not, back then if you could make cDNA libraries, everybody wanted you because very few people could do it. So Tom and I start talking. He said, "Yes, I'm starting a company. Maybe you should check it out." So, his company is Genetics Institute. It was started by Tom and Mark Ptashne, Tiny Mark, as some people call him. Boy, if he hears that—he already hates my guts. So, I said, "Well, I'd like to talk to you more about this." And one thing led to another, and I started to interview. It was literally not a company; it was a bunch of guys meeting. So I go to Boston, and we talk about this stuff. It's a bunch of people meeting in Mark's music room, which was actually Henry James's house, very nice house. We were talking. God, what shall we pick? What about Genentech, and how do we compete? Let's do gamma interferon because gamma interferon's hotter than hell. All this stuff—it was almost like a free-for-all. Brian Seed was there. Do you have his name yet?

Hughes: I've heard that name.

Lasky: Brian is this super genius guy who is a completely bizarre, Caltech kind of guy. He's Tom's graduate student, and he lives in the lab. He has a couch, and he has an old gas station pump. That's his décor, and he's sleeping in Tom's lab. And he's got hundreds of bacterial plates piled up.

Hughes: What was he working on?

Lasky: No one could understand what he was doing. He was doing crazy stuff which was useful but odd. Tom thought he was very, very smart. Tom has him in these meetings. We're talking, insulin and growth hormones are over. What can we do now? Well let's do gamma interferon because everybody wants to do gamma interferon. Well, let's do factor VIII. And Brian Seed said, "Forget it. Factor VIII will never be cloned. It's too big. No one will ever make cDNA's that big." That's Brian, okay? And we're saying, "Well, you know, Brian, you're smart, but maybe you're wrong." Nobody knew what was going on. It was really fun. [laughter]

Hughes: And it was all scientists?

Lasky: All scientists. Tom there, Mark there, and all these guys from [David] Baltimore's lab. Not all of them were great, but it was very exciting just sitting there, contemplating these things. For sure, if you talk to Dave [Goeddel], they were sitting around contemplating stuff. Could you do it?

So I started applying for jobs. I applied to Genetics Institute, I applied to Genentech because Lawn said, "You should really apply to Genentech." And I applied to Biogen and Amgen. I got offers from everybody. Now what do I do? Let's go into more detail here. This is kind of interesting. So Amgen was out because the science was terrible. I never was interested in Amgen, and I think that's still true, by the way.

Hughes: And that was your old friend Salser?

Lasky: Yes, right. But Salser really wasn't involved. He was kind of on the outs there.

Hughes: [George] Rathmann hadn't come yet?

Lasky: He wasn't there yet. It was '80.

I'm looking at all these jobs. Biogen I liked because it was in Geneva, and that was kind of cool but too far away.

Hughes: Did you—?

Lasky: I went there, yes. They were trying to make malaria vaccine. I was kind of interested in vaccines at that point.

Hughes: They were not into interferon?

Lasky: No, that was in [Charles] Weissmann's lab. That was all being done in competition with Goeddel.

Hughes: I see.

Lasky: I was talking to Bernard Mach. He was this guy who was interested in malaria. We were going to try to make malaria or some other vaccine.

Hughes: Does that mean Weissmann had a monopoly of the interferon business?

Lasky: No, I would say Weissman and Goeddel had the monopoly.

Hughes: I meant within Biogen.

Lasky: Yes, it was in his lab, mostly. It was more of an academic thing.

Hughes: For some years, Biogen, there isn't a physical place that is Biogen; it's a series of academic labs.

Lasky: Right. It was a small lab in Geneva, and then there was a place in Cambridge [Massachusetts]. And it was Wally [Gilbert]'s lab and it was Mach's lab and it was Phil Sharp's lab.

Hughes: And each of those labs was working on a different project.

Lasky: All different. One was hepatitis, one was insulin, one was interferon. They were interested in antibiotics, all kinds of stuff. And I liked the people there. This one guy, Julian—I can't remember his last name—was a nice guy. He was an English bacteriologist. I think he was VP of research or something. Anyway, it came down to Genentech and Genetics Institute. And I just said, "I'm going to Genetics Institute because they're giving me this huge hunk of stock"—I had like 1 percent of the founder shares—"and they're paying me more."

Hughes: You were going for the money—

Lasky: Yes.

Hughes: —because no company had a track record at the time?

Lasky: We'll go over why that was a mistake. [laughter] At the time, it was so crazy to think that somebody was going to give me all these shares of stock. Of course, I didn't understand what that even meant. I was getting peanuts as a postdoc, and my salary went up like three times over-night. It just was heady stuff.

Hughes: And it didn't bother you to be on the East Coast?

Lasky: Well, so it did bother me to be on the East Coast—a very perceptive question. In fact, there was no Genetics Institute when I started. I was the first guy who actually did experiments at Genetics Institute. But there was no place to do them. It turned out this guy, David Golde, whose name you may have heard many times, was a co-founder of Genetics Institute. Now, Golde is not what you call Maniatis, to say the least. He's not even close. Why was he even involved with this caliber of people? Well, it turned out Golde allegedly had a cell line, isolated from some leukemic patient, that made piles of gamma interferon. Everybody wanted to clone gamma interferon, so Golde was involved. He got shares of stock not because of his scientific input but more [because] they wanted his cell line.

So I said, "God, this is a pretty good deal." Where was I going to work? I was going to work in a little lab at UCLA. So I went back to UCLA, and they gave me this little tiny room. I had my own little centrifuge, my own little everything, okay? And a little desk. I could do everything in that one little lab.

Hughes: And the company, such as it might be, paid for the space?

Lasky: I think Golde somehow got this space because it was in the hematology department.

Hughes: Was there any stink about this kind of fusion of corporate and academic science?

Lasky: This was way before any stinks happened. Nobody in the academic world knew what corporate even meant. They had no idea what was going on.

Hughes: You were in an academic institution, being paid by a company.

Lasky: All my equipment was paid for by the company except my centrifuge, which I borrowed from Golde, and stuff like that. So here's the situation. I'm this one little guy, and my

project was to use these cells to clone gamma interferon and GMCSF [granulocyte macrophage colony stimulating factor] because they made that too. Now, up north is a different kind of guy, David Goeddel, who's trying to clone gamma interferon, and I know that. So you imagine this was not easy, okay? Nobody beats Goeddel.

Hughes: Was it clear to you at that point?

Lasky: I knew Genentech was trying to do it. Everybody wanted gamma interferon. That was the hottest thing at that point.

Hughes: But was Goeddel's name around as the cloner?

Lasky: Absolutely.

Hughes: Even then?

Lasky: Even then. I didn't know that as well as I knew it after I interacted with him. But he had tons of *Nature* papers already. He'd done insulin, he'd done growth hormones, he'd done a bunch of alpha interferons, and he'd done beta interferon. He was a huge presence in cloning, even at that time.

Hughes: Were you thinking anything about the fact that here was this young guy who had already made a name for himself and he was in a company?

Lasky: No, it was more I was impressed with him simply as a scientist.

Hughes: But it could have been encouraging to you.

Lasky: Oh sure, yes—the fact that he could do it in a company. Genentech at that time didn't strike me as being a company even. It was more like this group of guys who were doing molecular biology. They had no sales; they had no product.

Hughes: Yes, contract research.

Lasky: Sort of, yes. We'll get back to that because that's interesting, and how that place evolved because of Goeddel is interesting.

So what I'm doing is I'm making RNA from these cells, and I'm running them on sucrose gradients, and I'm taking fractions, and I'm injecting the RNA into oocytes. I had little frogs in my lab, and I'm pulling out these eggs, and I'm injecting into the eggs. In collaboration with this guy, Jake Lusis, who's a nice, smart guy, we're assaying the eggs for gamma interferon activity and CSF [colony stimulating factor] activity. Why? Because you want to find a fraction that has your activities so you can make your library from that fraction. Then you have fewer clones you have to go through.

Hughes: Was that obvious?

Lasky: Everybody did it that way. Yes. But unfortunately, what transpired was, I would get different data each time I would assay these cells. So one time I would get tons of gamma interferon. Another time I wouldn't get very much gamma interferon.

[Tape 2, Side A]

Lasky: They changed their phenotype all the time. It was just not very good stuff. Now, this was a big disappointment because literally the week or day or something I found this out, I opened up *Nature,* and there is "Genentech Clones Gamma Interferon."

Hughes: And your heart sinks.

Lasky: Yes, and I'm like, aw man, these guys are good. We got a *Nature* paper out of this experiment because we did show how big the message was for GMCSF. We showed that GMCSF wasn't just some fake activity. So the first paper from Genetics Institute actually is a *Nature* paper where I'm senior author, so that's kind of nice. That's what I got out of it.

But other things were coming out of Genentech, some of which I over-interpreted but nevertheless made me feel like maybe that's where I really want to be. So for example, I'm reading some other hot journal. They're making albumin in yeast, of all places. The Kern, as we use to call him, [Ronald] Hitzeman, is making albumin in yeast. And I'm thinking, God, albumin—that's important stuff, and if you make it in yeast, you can make kilograms of it and blah, blah, blah. And I thought, God, not only are these guys good cloners but they also really know how to make proteins in all kinds of different systems. So one thing led to another. I called Lawn and said, "How about getting my job back?" And he said, "I'll look into it." And they did it, they gave me a job. I don't know how that happened.

Hughes: So that's 1981?

Lasky: I was at GI for about eight months. End of '81, I'm going to Genentech. I started Genentech January 4, 1982. So the turnaround happened very quickly.

Hughes: Were there any sour grapes?

Lasky: I remember telling Tom I was leaving, and he was mad. He's not the kind of guy that reacts emotionally, but he kind of used logical arguments. Well, albumin is this, and we're going to be good too. But I said, "I don't want to move back East, Tom," because at that point, I was going to have to go to Boston.

Hughes: Did they have a building by then?

Lasky: It was the old Boston Lying-in Hospital. My lab was going to be the morgue of all places. I remember visiting it before they re-did it and seeing the slabs. It was kind of amazing. So Tom was disappointed. Mark, on the other hand, never forgave me. I think every time I see him, which has only been a couple of times, he doesn't even speak to me, which is really stupid. That's very short-sighted. But that's okay; I don't need him.

Hughes: Was there worry about information that you might carry to Genentech?

Lasky: We went over that. There were some lawyers involved. They can't stop you from going to another company, but they can stop you from transmitting information. So I said,

"Look, I'm not going to give them any information, besides gamma's cloned. What do you care?"

Hughes: Right.

Lasky: I started other projects at GI. One other project was bone morphogenetic protein project. That's actually turned out well for them. They have something in the clinic, and it has some efficacy, I think. But Genentech wasn't interested in that at all. In hindsight, I would have been okay at both places. GI has done well. I don't think they've done as well as Genentech, but they've done well. I don't think the personalities that I would have encountered at GI are remotely as potent in my life as the ones in Genentech, not even close. So I think going there was the right move. I lost a lot of money by not going to GI, but so what? I think in the long run it was not that big of a deal. I think it had a negative impact on the other guys in the company for a short time. They all did okay.

Hughes: Because their first scientist left.

Lasky: Yes. But they're all retired, and they all made tons of money.

Hughes: What was the hiring procedure? Didn't Swanson have to get into it?

Lasky: Yes. The first time I went to Genentech I gave a seminar, and everybody in research was at my seminar. I remember there were maybe thirty or forty people there. That was everybody. [Peter] Seeburg, Goeddel, [Arthur] Levinson, and Axel [Ullrich] were all there. Herb Heyneker was going to hire me to work on malaria vaccine because Herb was interested in that. So I guess they talked it over with Bob, and they said, "Yes, he's a good guy," and Bob said, "Fine." I was hired at a very low level, like the lowest scientist level.

Hughes: Swanson wasn't there?

Lasky: I don't think he was at the seminar. He was at other things I did.

Hughes: So your hiring was sort of a slam-dunk?

Lasky: Pretty much, because I knew how to make libraries, and I came from Caltech.

Hughes: Was Heyneker head of research at that point?

Lasky: Well, in name maybe, but Goeddel was clearly the golden boy from the beginning. Goeddel is the rock of the place. If Goeddel had gone to Cetus, Cetus would have been Genentech, and everybody knows that.

Hughes: What is that based on?

Lasky: For me, phenomenal intellect.

Hughes: You feel his intensity; I have talked with him.

Lasky: Yes, the intensity is enormous. The IQ is huge, and the drive combined with the IQ, that's what I like. I guarantee Goeddel isn't that much smarter than me. He might not even be as smart as me, but his drive is a thousand-fold higher than mine. He is the most competitive, driven person I think I've met, except maybe for Art [Levinson]. [laughter] But Dave as a hero kind of guy was so inspiring to someone like me.

Hughes: What about to his peers, like Heyneker? Who is really the first Genentech scientist, if you count the somatostatin research at UCSF. Then there's this young guy Goeddel coming in and taking all the—

Lasky: Herb can't focus on anything. He's the most unfocused human being I've ever met. He's just hyper—a million things going on. He's very smart but not focused, not capable of finishing things. The difference between Herb—well, a lot of people—and Goeddel is Goeddel can see the path much clearer than most people can. So Herb would be like going fifty different ways to get to the end. Dave would just go straight through, and that's the difference. I wasn't in that kind of peer group when I first got there. It took me a long time to get into that peer group. So I didn't know all the mechanics and the politics. When you think about who was there—Ullrich, Seeburg, Goeddel, Levinson—all four just gigantic egos and gigantically successful scientists. They all sort of bumped into each other, all working on different things. For me the most inspiring is Dave by far.

Hughes: Where does Dennis Kleid fit in?

Lasky: Well, that's an interesting question. Kleid is the guy that hired me. I ended up in Kleid's lab, and the day I got there, Lawn said to me, "Larry, within six months you'll be running this lab." That's exactly what happened. Dennis wasn't a clear thinker, for one thing. He had lots of things he was interested in but he never really read deeply or understood deeply. The great thing about Kleid, like Tobin, he would let people do whatever they wanted--in contrast to Dave who really is quite a control guy. Dennis really just let you do whatever you wanted to. Kleid's such a nice guy, too. He has this almost pixie personality, with his bright eyes. He's such a nice person. I remember sitting there. He's got this little original Mac on his desk. I'd never seen one. I said, "What do you want me to do?" He says, "Go into the lab and do whatever you want." I said, "Well, <u>anything</u>?" He says, "Just whatever you want." So I said, "Well, I'm in the vaccine department. Do I have to do a vaccine?" He says, "Yes, if you want." [laughter] So I get this little bench, and then that's it. That was great. Dennis hired Dave [at Stanford Research Institute]. The biggest impact Dennis had on Genentech was hiring Dave and bringing him to Genentech. That alone should give Dennis a gigantic place in the history book. That was the most important thing for the company.

Hughes: Remember that Goeddel was Kleid's postdoc at SRI. So here was his postdoc almost immediately at Genentech clambering over him.

Lasky: Right. I don't think Dennis took that badly. He understood immediately that this guy is a superstar and got out of his way. Dennis never did great science. He was in Tom Maniatis's lab and he had a few little things [publications].

Hughes: He was also in [Gobind] Khorana's lab.

Lasky: He was. But he never did great science at Genentech. I think Dennis's real talent was finding good people and letting them do their thing. He's not stopping them from being successful. He was good at that. He knew talent. He hired [Dennis] Henner, too. Now, Henner wasn't the greatest scientist but Henner was a smart guy and Kleid had a nose for science. Even somebody like me, I don't know that much about this guy but I think he's going to do okay. It wasn't like Goeddel where it was immediately obvious. It took a long time but eventually he was right.

Hughes: So you walked into a situation where the projects were exciting, and you were working with some of the superstars in this field. Is there another piece to this? I ask you, was there a drive to make this baby company succeed? How much is that figuring into your motivation?

Lasky: Not that much. I wanted to succeed, and I thought if I did something, then the company would succeed. But I had no idea what I was going to do. At the end of the day, what I did for the company financially—most people never generate income for Genentech. What I ended up doing for the company as far as income generation I would have never predicted. I didn't know what I was going to do, but I just wanted to be successful. I wanted to be like Dave. [laughter] That's what a lot of people wanted to be.

Hughes: That's a pretty tall order.

Lasky: Very few people, if any, became like Goeddel.

Hughes: Would you ever have been willing to work with that intensity?

Lasky: Probably not, because I had too many other things, like music, family.

Hughes: Were you married by 1982?

Lasky: Not at that point. Dave is so focused on science. I like lots of other things. I like literature, I like music, I like art.

Hughes: He, of course, had the rock climbing.

Lasky: But remember, rock climbing was like science for him. It was a huge challenge, and you could get killed doing it. The whole point was doing it even if you'd die doing it but doing it and being first to the top. That was Dave. I guarantee Goeddel wouldn't have been happy climbing on his own. He had to have somebody else who was as good as him so he could beat him. [chuckles] The dynamic between Art and Dave was quite amazing. The way they drove each other was phenomenal.

Hughes: Okay, so there you are at Genentech with a new bench and a malaria project.

Lasky: No, malaria was gone. Kleid said, "See ya." So I thought, well, what I'd really like to do is make a way that you can screen libraries of genes with an antibody. I thought the way to do that is you make some kind of viral vector with all the genes in it. You put a promoter in there so the bacteria make the protein, then you screen it with antibodies. So I said, "God, if I did that it would be useful for everybody here. It'd be a nice tool." So I started on that project. Turns out there was a guy down the hall, Harvey Miller, who

was a very unusual person. He was a bacterial geneticist. I started to work with him on this. He turned out to be this complete—he's very smart—but he didn't do anything. He sat in the hallway and pontificated. His nickname was Harvey the Hall Monitor.

So I started to build this thing. It's not going that well. Harvey's not being that much of a help, and I'm running into all these problems. So I said, what the heck, maybe there's some vaccine I can work on; I'm in the vaccine department. Everyone around me was working on foot and mouth disease virus. I thought, God, who cares about that? Why would anyone want to make an animal vaccine? So I go into Kleid's office, and I say, "What kind of vaccine do you think you'd like me to make?" He said, "How about one against sheep blue tongue virus." I said, "What? Okay, I'll read about it." So I start reading about it. This is over the first six months I'm there. I was thinking, I'll make some RNA and see if I can make virus and do a few experiments. Then I thought, this is boring.

Then I started reading the literature about herpes simplex. I thought herpes, now that's a big one. If you could make a vaccine against that that would be pretty good. So I start reading the literature, and as with many things at Genentech, someone in Dave's lab was working on herpes—Liz Yelverton. Liz was Dave's technician. She wasn't working on it, but she was getting interested in herpes. She had made a rabies vaccine kind of thing so she was kind of interested in vaccines. So we're kind of like, who's going to do this? Then I said, I'm just going to start working on this. By that point I had this technician, Don Dowbenko, who was with me the whole time I was there [at Genentech]. He was working with foot and mouth, and he got tired of working on foot and mouth. I said, "Let's make a herpes vaccine." He said, "All right." I said, "We need to grow it first."

It turned out because they were doing so many interferon studies they had herpes virus growing there because that was one of the viruses they tested interferon on. So I went down to somebody down the hall, Chris Czarniecki, and said, "You got any herpes growing?" She said, "Yeah." She gave it to me. So we're growing up tons of herpes virus in the lab. We have to make DNA. So I read the literature, and I found that this specific gene called gD, glycoprotein D, might be a good target for a herpes vaccine. So Don and I, we'd better purify the DNA so we can make this gene. We're making the virus; we put it in the centrifuge; we share the centrifuge with Seeburg; we're spinning the hell out of this thing. The tube explodes. Herpes virus all over the centrifuge. It actually wasn't the virus, it was the DNA for the virus. So we cleaned it up. Seeburg regained control. He smoked four or five cigarettes, which he was constantly doing, and everything was fine. We got the thing made.

This is where the new concept came in. This was due to Levinson. So Levinson had gotten there. Levinson was this guy who was hyper as hell and super brilliant, but he was working on oncogenes, and what good are they? It was kind of not clear what he was doing, but we knew he was really smart. Unlike everybody else, he could actually put DNA into mammalian cells and manipulate the DNA, and he had all these vectors.

Hughes: Had he brought that technology from UCSF?

Lasky: No, he actually derived it there. He was a maniacal plasmid maker. His lab bench, by the way, was the worst of all. There was a little place in the middle of it, and then there

were piles of bacterial plates and tennis shoes and shirts—all kinds of stuff. He would work in a space about this big [Lasky gestures one foot] in the middle of this mass of stuff—just a wild guy. But clearly this guy may be like Dave. We weren't sure. Maybe this guy is as smart as Goeddel even. He was very arrogant at that time, by the way.

Hughes: Was he?

Lasky: Yes, he changed a lot.

Hughes: He knew he was good?

Lasky: He knew he was very smart, and our relationship changed a lot over the years. At first, I was like this nobody, and now it's different; we talk. We're more peers. Back then it was like you were in one of two bins with Art, stupid or smart. Dave was in the smart bin, but everybody else was in the dumb bin, okay? [laughter] That was Art back then, but he changed a lot.

What was really fantastic, and this was very new stuff back then, was Art was actually talking about making proteins in mammalian cells. Most people thought mammalian cells would never be useful for that because of the expense and they're very fragile and you can't grow them in gigantic fermenters. You have to grow them in these tissue-culture bottles, and nobody thought that would ever work. But Art said, "Let's work on it; see how it goes." So he started to make all these plasmids, and we're trying to make this herpes protein in bacteria. It's not working. It's all falling apart. It gets degraded. It's a mess. Then I go to a seminar, I think by Art. He starts talking about hepatitis and how you can make hepatitis antigen in mammalian cells. I thought, God, it's amazing. You can actually make an antigen in its native state without the virus around. That sounds perfect for a vaccine. We were the first people to do this.

We took this glycoprotein D gene, and I go to Levinson and I say, "Do you have some plasmids that we can stick this thing in to make in mammalian cells?" He says, "Yes," and hands me this book with hundreds of plasmids in it. We go through the book and try lots of different things. Lo and behold, we were able to make this protein in mammalian cells. It's secreted, and it's folded up right, and it's got sugar on it. It looks exactly the same way as it does on the virus. So that was very exciting because the only other people who had done that at that point were [Joseph] Sambrook, and I forgot the other names. They did it with flu, and it's useless for a flu vaccine because flu forms a very complicated oligomer of three proteins. Theirs didn't form that whereas ours was a monomer, and so it was much more useful. So we were able to make a lot of this protein. But then what?

Hughes: So is mammalian cell culture only happening at that time in two institutions?

Lasky: Pretty much. For making recombinant proteins, it's actually happening for real in one institution, Genentech. And that was Levinson, solely Levinson. He pushed that. I would say, until recently, that's his great contribution to Genentech.

Hughes: How does yeast enter this picture?

Lasky: Yeast also will make mammalian proteins, but the sugars are different. They don't secrete very well. Things just aren't made quite as well as they are in mammalian cells. You can make hepatitis surface antigen in yeast, and in fact, that's how Merck makes their vaccine, in yeast. But the antigenicity, that is how immunogenic it is, is not as good as the mammalian cell stuff. In fact, that was a huge breakthrough. It was timely for us. It was also timely for tPA [tissue plasminogen activator] because at this very same time tPA was being cloned, and there was no way to really make it. When it was made in bacteria, it was inactive. Again, Levinson to the rescue. He made it in mammalian cells; you get great expression.

Hughes: Was tPA at that stage recognized as a big project?

Lasky: It's a huge project.

Hughes: So Genentech knows the potential there?

Lasky: Yes. On the negative, there was a lot of hype. There was always competition at Genentech for projects, right?

Hughes: That's why I was surprised—the way you told it—that you could decide you were going to work on X vaccine and that was all there was to it.

Lasky: Right.

Hughes: Think of that happening today.

Lasky: Oh, no way. Back then, remember, anything was new and anything could be perceived as useful. We didn't know and so why not?

Hughes: I would still have thought that at least you would have had a presentation to Swanson.

Lasky: No, in fact, I remember making presentations to Swanson about herpes later. To make a long story short on herpes, we made the protein. This guy [Philip] Berman came along and helped us out. We made a guinea pig model and lo and behold, this thing protected guinea pigs from herpes infection. Unbelievable result. It got in *Science*. It was on TV. It was the first time I got on TV. It was just a huge result. Everybody said this is the vaccine for herpes. Now, I presented this to Swanson. You know what Swanson said? "Can't you make something that helps people who already have herpes?" Anything Dave was working on, Bob was interested in as opposed to anybody else. Anything certain marketing people like Jim Gower told Bob was great; Bob was interested in it. Bob, like a lot of people, had biases. Dave was a big one, and Jim Gower's marketing input was a big one. Bob was terrified of vaccines because vaccines are the only drugs that are injected into healthy people, so liability is an issue. Of course, the vaccine I was making and Levinson was making, there's no virus there. It's just a protein. What could be safer?

Hughes: But Swanson must have understood that.

Lasky: I'm not sure he understood it well enough to accept it. Now hepatitis has killed tPA as far as sales. Hepatitis is billions of dollars a year. TPA is about $250 million a year. So,

in hindsight, vaccines are a much bigger market than tPA ever was. But back then, tPA was going to be used in every single patient with myocardial infarction. Every patient was going to get it. We were thinking every heart attack, they get a squirt of tPA, it lyses their clot, and they get off the table. Genentech was going to make billions of dollars off of this. So that was the bias. That was the marketing scheme.

Hughes: In terms of the sentiment against vaccines, was it mainly about the liability?

Lasky: Yes, almost purely. Marketing, sales, was an issue too, but that was before vaccines were mandated. Hepatitis vaccine has been mandated. Every kid gets a hepatitis vaccination. Herpes will be mandated if it's successful, why not? Why spend all that money on drugs if you're vaccinated and you don't get herpes. Long term, it's a much better way to go. So a lot of these vaccines will be mandated, which means every kid gets a $100 shot.

Hughes: I heard that for some of the big pharmaceutical companies, it's more than just the problem of liability. It's the fact that if you have a really effective, preventive vaccine you maybe get it once, whereas a good therapeutic product you hope will be used until people drop dead.

Lasky: Yes, but long term vaccines still are the most effective way to treat infectious disease.

Hughes: I have no doubt about that. But are they money makers in comparison to therapeutics?

Lasky: Well, GlaxoSmithKline makes billions off of hepitatis. GlaxoSmithKline took our herpes vaccine and have now spent seventeen years putting it through the clinic, the one that I made. So, you can make money off of vaccines if they are mandated. Remember, every single kid under the age of seven or eight. If you just do the math, how many kids are born every year? You can charge a hundred bucks a shot. It's millions of children get a shot every year. They don't get the shot the next year but there are millions more kids coming along.

[Tape 2, Side B]

Lasky: We pushed the herpes vaccine to the point where we were very successful. At least a couple of *Science* papers. It started to raise me a little bit, but mostly what it did was point out the fact that Genentech wasn't too interested in vaccines. That didn't stop me from doing the next one. Eventually Genentech sold it. They got a few million up front from SmithKline. SmithKline, I think, last year announced that the exact same vaccine we made had inhibited 70 percent of all transmissions. So that's a big deal. In fact, it will probably be approved by the FDA, but it will be almost twenty years.

Hughes: Backtracking, why did you end up in the vaccine department? As far as you told me, you hadn't had any exposure to viruses, had you?

Lasky: No. I think I just ended up there because that was where Kleid was, and Kleid had an open position, and that's how it happened.

Hughes: You didn't mind?

Lasky: I didn't care. I worked on lots of different things. I always liked to work on something new all the time. So vaccines sounded just as good as anything.

Hughes: What about the safety aspect? The NIH guidelines were winding down by the time you arrive at Genentech, right? Were they a hassle?

Lasky: Not at all. Zero. In hindsight, I think we weren't nearly safe enough. There was radioactivity all over the place. There was ethidium bromide all over the place. There was herpes virus, which isn't deadly. I don't think we were safe enough. I'm not saying anything against Genentech. Very few people were being safe in those early days.

Hughes: Was there an oversight committee of some kind?

Lasky: Not that I remember, but we had a P3 [physical containment 3] room. I don't know if it was an approved P3 room, but we did have a room where we could do biohazard-type cloning.

Hughes: Did you have to do herpes cloning in there?

Lasky: No, bench. I just remembered a funny thing about the herpes. The little piece of gel that contained the gene, I dropped on the ground in the dark room. I remember I just picked it up and washed it off and made the clone out of it. That's the one that's actually been put in people. Well, the DNA's long gone already. It's been replicated zillions of times. So that was all done just on the bench. We did the viral work in the fume hood, and we wore gloves. But nobody ever wore lab coats. It was macho city there. You weren't supposed to wear lab coats.

There were other aspects of political correctness that were completely different then. Tom Kiley came in and brought a poster of a topless girl drinking beer and gave it to us. He was the corporate attorney. There are a million of other stories like that of things that went on.

Hughes: I've heard some of them, but tell me one or two more.

Lasky: [Philip] Berman liked going to Hawaii, and so he put this picture of this girl drinking a Coke out of a coconut. It was looking up at her, and the coconut juice was running down her chest. It was just—no thought police, no nothing. There were other funny stories, like Rick Derynck, who was Goeddel's scientist. He was European but sort of a Renaissance period guy. In other words, he never bathed. [laughter] He walked in the dark room once, and Liz Yelverton went in after him and said, "I'm not going to work with this guy anymore. I can't even go in the dark room, he smells so bad." Fred Ruffin was our one human resources person. He had a talk with Derynck. He said, "You know, in America we bathe all the time. You have to bathe more than once every few weeks." He helped him clean up.

I remember my interview with Goeddel—there was a little radio-controlled car that drove around his office and went out the door. It was really fun. It really was like a fraternity house. We were all single. We worked all the time. Saturday night the place was packed.

Hughes: But you said you had other interests. So you weren't there all the time?

Lasky: I didn't work nearly as hard as those guys, not even close—Goeddel much more. Goeddel lived close by. I lived in the city, and he lived in Hillsborough.

Hughes: There wasn't any pressure to get Lasky in there more often?

Lasky: No, Goeddel and Levinson always had this funny thing about me. It was this ratio. The numerator was productivity and the denominator was intellect. Derynck had the highest number. In other words, his productivity for intellect was enormous, and I had the lowest. [laughter] They thought, yes, he's smart, but he's lazy. Yes, he gets a lot done, but it's pure luck. That's what they always used to say about me.

Hughes: You mentioned the interaction between Goeddel and Levinson.

Lasky: My perception of it was, colleagues but competitors. No doubt Seeburg and Ullrich and Lawn and all these other guys were very accomplished big guys. But to me those guys were way out on the curve, the two of them—way, way out and many standard deviations away from the rest of us. So they were kind of competing all the time. When they worked on ras, Dave got some credit for ras, and Art, I could tell, wasn't happy about it. So I thought that competitiveness drove the two of them, but they respected each other. I think those two had more mutual respect for each other than any group or pair.

Hughes: Would you say that they are friends?

Lasky: Yes. When [David] Botstein had his going-away party, I went to his going-away party. I could still see Art's got a soft spot in his heart [for Dave]. Art doesn't have time for most people anymore, but he's got time for Dave. I think they're two super guys, and they've done incredible stuff in their lives, and I think they both realize that about each other. Those kind of people, I'm not sure if affection is in their vocabulary, but certainly mutual respect is huge for those two. I think if Art will see somebody, it's Dave any time or vice versa. Art in the long run probably has done better than Dave. Certainly Genentech is way, way better off than Tularik. They're having trouble, and part of that I think is because as phenomenal of a scientist as Dave was, he wasn't that good at product development and product choices, even sort of biological thinking. He was much more of a molecular kind of thinker. I think a lot of that is part of the problem at Tularik.

Hughes: Other people have said that at a certain stage it became clear that Genentech needed more biology. So if you suppose that Swanson was particularly listening to Goeddel, the argument could be that all you have to do is isolate the gene and clone it.

Lasky: Absolutely true. There were many problems because of that. TNF [tumor necrosis factor] was the classic example of that. Well, it's got a great name—tumor necrosis factor. What could be better? Well, the biology of that molecule is phenomenally complicated, and the concept that we were going to squirt this into people and lyse their tumor was <u>incredibly</u> naïve. Even at the time it seemed to be totally naïve.

Hughes: Were some people saying that?

Lasky: There were two things going on, lymphotoxin and TNF. Whatever Dave wanted, that's what happened. It was very hard to stand up to him. Bob sort of wouldn't. I think in the early days when all you had to do was clone obvious stuff—growth hormone, insulin, and even tPA—it was okay to be just a cloner. Certainly growth hormone and insulin are the most simple-minded in that respect. But as things got more complicated with cytokines and interferons later—as biology got more complicated and the immune system got more complicated, just cloning stuff, all the low-hanging fruit was all gone. Factor VIII and factor 9 were the last ones--what I call the replacement therapy stuff. Then it got very complicated. Then it got much harder to do the right thing. That's why I think we had a long hiatus at Genentech in the early nineties.

Hughes: Would you say that Stebbing was brought in as an antidote to this lack to biology?

Lasky: Yes. The problem with him was he wasn't a strong enough scientist to do that.

Hughes: Meaning that he still had to counter the idea that all we have to do is clone it?

Lasky: Yes. Remember, Genentech really was a cloning company. So it was in the right place at the right time. Its phenomenal success was in large part due to the fact that nobody else could clone. Nobody could make oligos. The fact that you could go to this guy Mark Vasser and tell him you wanted oligos. Nobody elsewhere could do that. Mark Mateucci was a huge influence there. It just was a luxury to be able to do these sorts of things. It was very hard for other people to do it. That got the rocketship going. But the rocketship kind of faltered when the biology got in the way. That's what happened, and it got very tough. Now, what saved it was monoclonal antibodies. That's what's gotten it back on its feet.

Hughes: Was this a common mindset of those very early companies? You did recombinant DNA and you wanted these obvious products. For Amgen it was Epo[gen]. But people must have been thinking ahead and saying, "After Epo, after insulin, after growth hormone, what's next?"

Lasky: Yes. What was next were the cytokines, so gamma [interferon], TNF, all these cytokines. Remember, on the cover of *Business Week* was gamma. That was going to be the next big thing. But that's where things stumbled because those things were phenomenally more complicated. First of all, they don't work systemically; they work locally. So a T-cell secretes a tiny bit of gamma interferon when it wants to. It's not everywhere. That's where Genentech stumbled. They thought, well, it's like growth hormones. We'll squirt it in, and we're going to make a billion bucks. That was the problem.

Hughes: Was everybody more or less thinking that way? Not realizing the complexity?

Lasky: Pretty much. That's why there was this lull. In fact, if you look carefully at the biotech industry, there's this first bolus of drug, the obvious stuff. Then there's been this lull. Really, all that's working now are monoclonal antibodies. Pretty much that's it. Nothing else is working. Small molecules, that's been big pharma for years, so they can't call that biotech. So if you look at the history of this, the obvious stuff was done, and then nobody knew what the hell to do for a decade. And then Paula Jardieu, who was an important person at Genentech, pushed monoclonal antibodies at Genentech. Dave

didn't come up with Herceptin or any of that stuff. He was long gone by the time all that monoclonal antibodies stuff happened. That's the new wave, which I think actually will be much longer. The biology there is more simple-minded. There are a lot of challenges. It wasn't just Genentech. Everybody didn't know what the hell to do, except that there were these popular things to clone, like TNF or gamma or these kind of things. They were popular because there were papers in not such good journals which suggested they would be good for treating cancer and all kinds of things. But those studies were pretty bad.

Hughes: Remember the media is a factor in this too—

Lasky: Yes, terrible.

Hughes: —raising expectations.

Lasky: Everytime I talk to them, and I read what they say, I wonder is this what happens all the time? So when they interview Rumsfeld or whoever, do they screw it up this badly? Just when they talk to a scientist do they screw it up this badly. I think it's just really a disaster.

[End of session]

INTERVIEW 2: JULY 3, 2003
[Begin Tape 3, Side A]

Lasky: One good thing was Dennis Kleid was my boss but really never told me anything to do. I've never had a boss really. Dave Goeddel was my boss for a little while, but I think he finally gave up and just said, "You can't be controlled. Why don't you just go to Steve Shak. He'll leave you alone." I'm not the kind of person that can be told what to do. It just doesn't work with me. I'm a very independent guy. I just bristle when somebody gets in my face. I'm a successful guy. I don't need anybody to tell me what to do.

Hughes: Was that unusual to be so independent at Genentech?

Lasky: Certain people liked to be that way. Certainly Axel Ullrich and Art and Dave and all those guys were that way. But I think there was this weeding-out process where if you were a young scientist there, you either became a follower or a leader. That was kind of my problem at Caltech. I just couldn't stand being told what to do. It's not my style, so I decided to go on my own and figure out something. In this little project I did first, I tried to make these libraries. You could screen for the production of the protein so you could use antibodies to isolate new genes. That was sort of the first thing I tried to do, but it became just too difficult to do all the bacterial genetics and everything. It only took a few months to figure that out.

I was in the vaccine department. There were several projects going on but the main project was foot and mouth disease, which was the project Dennis Kleid was doing. This always occurred to me as kind of a silly thing to do. There was no foot and mouth disease in the United States. It was an animal disease. I didn't want to make an animal vaccine. That seemed very boring. They were doing it in *E. coli.* They got a big *Nature* paper out of it, but it always seemed to me to be boring stuff.

Hughes: Do you know how the project arose?

Lasky: I think Kleid knew Howard Bachrach who somehow got into the National Academy of Sciences. I never understood that, but he did. He was this foot and mouth guy, and he was a friend of Dennis's. I guess foot and mouth is a problem in other parts of the world. They thought they'd make this vaccine very cheaply in *E. coli,* and it would solve the problem. There were a few other things going on. Hepatitis B vaccine was going on, which was more exciting because it was a big human problem.

Hughes: Also very competitive.

Lasky: Very competitive, yes. There was already a vaccine out there made from a serum which was not a very good vaccine. It worked but it's a hard way to make a vaccine. Chiron and Merck were trying to make the recombinant vaccine in yeast, and this was a big project that Bill Rutter started. In fact, how Chiron actually started was that project.

As I told you earlier, Art Levinson used this whole concept of making a hepatitis vaccine in mammalian cells as a way to develop mammalian cell technology at Genentech. As usual, Art was brilliant enough to kill two birds with one stone. He made a great vaccine, but he also figured out how to use mammalian cells to make proteins. This was something nobody ever thought would be done because animal cells are

finicky, and they're expensive, and they require serum. You can't grow them in big batches and all this stuff. Everybody just never thought they would be done. As you heard from Goeddel and you'll hear from [Diane] Pennica and all the others, that's how tPA was eventually made. It's the only way tPA could have ever been made. Art's huge contribution to the company was to convert it all over to mammalian cell technology.

Hughes: Do you think he had any idea of how fruitful the technology would be?

Lasky: Probably not so much. Art looked at it as more of a scientific challenge. That's how he looked at everything. He also felt like he wanted to contribute to the company, but he didn't want to look for a gene to clone or something like that. He was our resident expert on mammalian cell biology. Nobody else knew remotely. Goeddel and everybody else were mainly bacterial guys. So Art took it upon himself to be the center of this whole thing. He did actually convert Genentech over into mammalian cell biology.

Hughes: Did Art or anybody else at that time foresee that there would be products down the line that would not work in *E. coli* or yeast?

Lasky: I think that was the concept. He understood that, but exactly how useful it would be I don't think he totally understood. For antibodies it's been indispensable. You absolutely can't make real antibodies in *E. coli*. It's just impossible. You can make them, but they don't work very well. So for things like Rituxan or Herceptin or Avastin, these were all made in mammalian cells. That of course would have never been predicted at the time. Nobody even thought about antibodies really as a drug. Then, of course, having all that infrastructure to make proteins and mammalian cells made it much easier to make antibodies.

Hughes: Is it a conformational problem?

Lasky: It's assembly and conformation. Remember, an antibody is four separate chains, and all the chains have to fold up right. Then they have to all come together, and it's disulfide linked and protein-protein interaction. The combining site is a combination of two different chains. It's a very complicated molecule, an antibody.

Hughes: And *E. coli* just doesn't make it?

Lasky: You can make it, but it's one divided by a very large number as efficient as it is in mammalian cells.

Hughes: Does this explain why some of those early antibody companies had a really rough time?

Lasky: I think it's in large part. The targets weren't there. Nobody knew what targets to do. They were infectious disease targets that were straightforward. Nobody ever dreamed that an antibody against a B-cell antigen like Rituxan would become a huge drug. That was way, way later that that became clear. So in the vaccine department, you were kind of looking for something to capitalize on—a new vaccine and then maybe do it in mammalian cells and all this stuff.

Herpes simplex virus seemed to be something. It was a very big disease. There were not vaccines for it. Acyclovir came much later. The mortality isn't large but the morbidity is huge. Ninety percent of us have herpes simplex type one. A large number of people have type two, genital herpes. So I thought, well, this is probably a good vaccine to try. The other reason was, there was a paper that had come out by a guy named Richard Dix who is over at the V.A. [Veterans Administration Hospital] in San Francisco. He and some others had shown that a monoclonal antibody against a specific cell surface protein called glycoprotein D would kill the virus, would neutralize the virus. This is exactly what you want because unlike a lot of other viruses, like polio or foot and mouth, the herpes virus is very complicated. There are tons of different glycoproteins. It wasn't at all clear which was the right protein to pick. So this paper told us gD was the right protein to pick.

Once we knew that, it just became a matter of cloning it and expressing it and seeing if it worked. That turned out to go pretty fast. We had to learn a lot of stuff from scratch. Nobody was growing virus to the large extent we were. As I related earlier, the first time that we grew the virus we were making the DNA and the tube blew up in the centrifuge. People thought that herpes was all over the centrifuge. It was actually the DNA of the herpes so it was safe, but people went crazy. Peter Seeburg said, "I'll never touch that centrifuge again." It was kind of amusing. People weren't used to infectious agents in Genentech at the time, other than stuff they were using for interferon. With interferon, of course they were using viruses to assay the interferon. We were growing a big quantity of this stuff—roller bottles of virus—and that freaked people out.

Hughes: Did Genentech have a policy about biohazard?

Lasky: There was the usual don't pour P^{32} down the sink. If you have an infectious agent, be sure you add bleach. These were very early days though. There were unknowns about cloning viral genes and whether that would be dangerous. With herpes we pretty much did it on the bench top. AIDS was much different. With herpes we pretty much did it on the bench top.

Hughes: Did it ever give you pause?

Lasky: No. There was a macho atmosphere at Genentech--no lab coats, no radiation badges, mouth-pipetting phenol. That actually got Dennis Kleid very badly once. He never worked in the lab much, but he came back in the lab to do some project. We took a picture of him mouth-pipetting some phenol and the very second after we took the picture it went in his mouth. It's horrendous stuff. It destroys proteins instantaneously. So he had this bleached white skin on his chin for a few days. It was funny. It was a macho kind of place. Nobody wore lab coats. I remember you just never did it. People were doing P^{32} without using a radiation badge. Some guys like Seeburg were smoking cigarettes and running sequencing gels at the same time. No rules, a ruleless society in many ways. There are other stories about that. People were just doing what they wanted to do.

Hughes: The Genentech scientists were predominately molecular biologists by training?

Lasky: Almost completely molecular biologists.

Hughes: I remember from reading the literature about the recombinant DNA controversy that people who came out of the microbiology tradition were horrified at how little molecular biologists knew about safety techniques or just plain ordinary bacterial culture.

Lasky: We didn't care about that stuff. We wanted the gene out as quickly as possible, and nobody really thought about danger. In fact, most of those dangers were really meaningless. Nobody ever got sick, and nobody ever came down with some horrendous bacterial infection or any of that stuff. I think the reagents like phenol and ethidium bromide and radiation are much worse. Who knows what the long-term repercussion of exposing all of us to that crap was. But I think the other stuff, like the viruses, wasn't nearly that bad. Although in AIDS, as I'll tell you, it was a little different.

So I started from scratch. I did this whole thing—me and Dowbenko who was my technician the whole time, a great guy. Would do anything I told him to do, and he's really a great technician. Started from scratch, cloned the gene, sequenced it. Back then, sequencing was very difficult. We did Maxam-Gilbert, this terrible thing. Actually, they won the Nobel Prize for it, but I was never sure why. It was an awful way to sequence DNA.

Hughes: Why didn't you use the Sanger method?

Lasky: Well, because Sanger was just starting. Seeburg was just getting it going. It wasn't a standard technique. We're talking 1982, and there was a battle between Sanger and Maxam-Gilbert. A lot of people were still using Maxam-Gilbert in those days. It was a really awful technique. You had to do it in the hood. There were a million steps, and reading the gels was a pain. We did it that way, though. We sequenced a few genes that way. And then, how are we going to express this thing? We tried some *E. coli* stuff but it never looked really good. Then we thought, Levinson's doing all this hot stuff with mammalian cell expression. What we really wanted was the protein to look as much like it looks in the virus as possible. Three criteria: folding it up right, coating it with sugars right, and secreting from the cell so we could easily purify it.

Hughes: How had you arrived at those criteria?

Lasky: Well, mainly by logic. When you make a protein in *E. coli,* because it's not normally made in *E. coli,* it just doesn't look right—other than small proteins, like insulin and growth hormones, many of which had to be re-folded to get the right conformation. A big protein like this, this was 300-400 amino acids, just didn't seem like it was going to make sense to make in *E. coli.* Now, everybody else was trying to make vaccines in *E. coli* at this time—everybody. Only my lab and Levinson were doing it in mammalian cells.

Hughes: Well, Chiron was doing hep B in yeast.

Lasky: That was the only different way. Hep B is a different kind of antigen in that it self-assembles to form a particle. What they found was in yeast it did self-assemble, but it didn't get secreted from the yeast. So they had to lyse the yeast and purify the particle, which was a mess. And we thought since proteins normally are secreted from mammalian cells that we would take advantage of that because then we could

engineer—this was truly one of the early engineering feats—the protein to be secreted from the cell to the media. We wouldn't have to lyse the cell; we could just take the media, which is a huge advantage because you don't have all that garbage from the cells.

Simultaneously, Joe Sambrook and Mary[-Jane] Gething did this with influenza. Influenza was probably the viral protein about which most was known, the neurominadase. We read these papers, and we thought, this is kind of what we want to do. The problem with influenza is it forms a trimer, and it's a complicated protein. We didn't think they would be successful. In fact, ultimately, they weren't able to make a vaccine that way. What they were trying to do was too complicated. We thought maybe we could chop off the tail of the glycoprotein D, which is what sticks it to the cell and gets it secreted. Then all we have to do is purify it from the media using some kind of a sedimentation column, and we'll have pure protein. And that's exactly what happened.

Hughes: Were you figuring this all out?

Lasky: Mainly it was me and Don, but of course I'd go to Art and Chris Simonsen, who is another guy there, and say, "What plasmids should we use for this?" They were doing a lot of amplification work where you could amplify the levels of protein expression. This is all Art's famous stuff that now everybody uses. We could just go down the hall, and I could get these plasmids. That was very convenient. We were coming up with all this—I was coming up with all these ideas. At that point, Berman was there, and he was going to be the guy that helped with the vaccine because he had more expertise in making antibodies and stuff. The molecular biology was all being done by me. I was making all the plasmids myself and with Don's help. So I was basically doing all of it. Lo and behold, we make this thing, and it gets secreted. We say this is going to work. At least we're going to make a lot of protein.

We then had to figure out how do we figure out if it works? We could do a simple experiment which is give the protein to Berman, and Berman injects it, with Freund's adjuvant, into guinea pigs and rabbits and all kinds of stuff. Then we make antibodies and test it in vitro assays whether we can kill the virus. We could; we could wipe out the virus. We got these enormous neutralization titers using this recombinantly made protein. This was very exciting stuff at the time. Nobody had really done this with a herpes protein. Other people were doing it in *E. coli*, but they were getting lousy titers and it was very hard to purify. We thought we were going to blow these guys out of the water. But we were nobodies. Nobody was paying attention to us. Our papers were appearing in junk journals like *Nature Biotechnology* or stuff like that. These guys were getting it in *Science* because they were all well-connected guys. This was a recurring theme in my career: These well-connected guys got in better journals, but oftentimes I did better stuff. I was the new guy. This was my first thing I did on my own.

Hughes: It wasn't enough that you were coming from this great cloning organization, Genentech?

Lasky: No, that wasn't enough. We were nobodies in the herpes field. There was this very powerful, very unpleasant man named Bernard Roizman who was the king of the herpes field. He owned the field. Every paper that came out was from his lab. All the people who worked in the field were from his lab, and then along come these cloning punks. I

remember sending the initial paper, showing we could make neutralizing antibodies this way, to *PNAS*. He said, "Oh, I'll take it on," because he was in the academy. They basically squashed it, kept it quiet. He said,"Well, the reviewers don't like it." I said, "How can they not like it? What are you talking about?" Obviously, it was political. He saw competition, and he squashed it. It was very obvious what was going on. But we got him back in the end.

Then we had to go to another model of herpes. Remember, I'm a molecular biologist trying to figure out how to do animal work. So we decided we would try mice. In fact, if you inject mice with herpes, you can kill them. So we thought this is kind of an interesting animal model. It's not what really happens in people. What happens in people is they get a genital infection that resolves. But at least we'll know in some sort of in vivo system whether our vaccine can work. So we got some mice, and we ordered some herpes virus that we knew would kill mice from an outside contract group. We vaccinated the mice. Lo and behold the vaccinated mice were totally protected. The other mice were dead as doornails. We thought, this is getting better; we're doing real vaccine stuff here. This actually appeared in the first paper. So not only did we show we could induce neutralizing antibodies with this completely genetically engineered protein but we could also protect mice from herpes infection. I thought that was pretty good, but Bernard Roizman disagreed. He's a famous guy, so what are you going to do?

Hughes: You were going to send it to another journal?

Lasky: Well, yes. That's all we could hope for.

Then we decided to try a different model which was much more realistic, the guinea pig genital model. Again, I'm a cloner. How do I do this? So I asked around, and it turned out Syntex, which is the old company in Palo Alto which [Hoffmann-La] Roche ended up buying, was doing some herpes work. I called this woman up, Debbie Epstein, and said, "Can you teach me to do this model?" She said, "Yes, it's easy. I'll show you how to do it." So I went down there. She said, "Put some sodium hydroxide on their genitals, and then you squirt some herpes [virus] intravaginally. In a few days, they get a raging herpes infection. I said, "Well, I don't have one of these needles," because it was a special needle. You can imagine you can't go in there with a real needle because you'll poke them. It turns out, there's this little needle with a ball on the end. You could shove it in there, and it didn't hurt them. So she gave me the needle. I remember for years after that I kept this needle on my lab bench just as a reminder of how much fun this was to go from cloning a gene all the way through to demonstrating in a real animal model that something worked. This was something really great that we did. We did it all in two years. It was incredible how fast it was. That was the power of Genentech—you could do things that fast.

So then we had to go against some bureaucracy at Genentech. There were some rather conservative people. By this point we had a safety person. Carol Grombach was her name. She slowed things down dramatically. Her job was to create problems which she could then solve. This sort of person I've come up against many times in my career. In fact, Jack Obijeski, who was the head of the vaccine department, was a classic person like that. He would create problems which he could then solve. And I hope you read this, Jack. So she stood in our way: "You can't do these experiments. We're going to

have herpes all over the place, and they're going to shed." I said, "We have to do the experiment. We'll have to come up with a way to do it." There was this great guy in the animal facility named Dietrich Craze, and he said, "Well, maybe we can make a cage." So finally we figured out a way to do it that would satisfy her. It took months. It was really bad. It took us longer to do that as it did to do all the previous work.

Hughes: You didn't think, maybe I should go talk to Bob Swanson?

Lasky: No, I didn't talk to anybody about this stuff. Bob didn't even really want us to do this. Bob, as I told you earlier, was not interested in vaccines. We were doing this just because we were in the vaccine department. It was very exciting stuff. We were getting data. We were doing new stuff.

Hughes: Even though the administration had not chosen vaccines as a line of work, you had come up with something that looked really promising and was a product and a potential moneymaker.

Lasky: A blockbuster, yes. I think that's what allowed them to let us do it. They really didn't like that we were doing it, but they were saying, "Boy, something's going on here. We better see how this works out." Dennis Kleid, bless his soul, had a lot of fights with Bob about a lot of things. I'm sure Dennis was in there, and Jack Obijeski was in Bob's office, saying, "Leave these guys alone. They're doing great stuff." I'm sure there was a lot of stuff that was going on that I wasn't aware of. I was just doing the science. I'm sure that they were lobbying for us the whole time.

Don and I said, "Well, we have to titer the virus." We went up there, and we did this guinea pig thing. We wanted to find out would this model work. We didn't do any vaccination at first. We just ordered some guinea pigs and we used various doses of virus, a classic microbiology experiment. We took several groups of eight guinea pigs and gave them increasing doses and then we observed them. I remember the first time I did it, because remember, I'm used to cloning. It sounds bad, but this was what it was. These guinea pigs are asleep, and I've got them lined up with their legs spread apart. I'm shooting this stuff in them, and I'm picking them up and shaking them to make sure the virus is getting—this is how we were doing it. We don't know what's going to happen. Like four days later we go up there, there's herpes everywhere. They are just messed up. I go down to Phil [Berman] and say, "You know, we've got an animal model here. We're going to figure out if this stuff works real soon."

Hughes: Are you getting to be a little nervous about all this?

Lasky: I just detested doing it. I didn't like hurting the animals. They looked bad; they were miserable. I hated that. Every time I'd go up to the animal facility and come back down to the lab, I'd feel sick to my stomach that I had done it. You know what? I said I don't care. I'm going to do whatever it takes to figure this out, and that's the way I was. Nothing was going to stop me. I felt like crap, but I thought it's worth it. We're going to really figure out if this stuff is a vaccine.

Hughes: You felt like crap at one level, but you also were elated because the science seemed to be working.

Lasky: Yes. I felt sick to my stomach, but then I thought, let's get this stuff formulated and get into those guinea pigs and test it. So, we did the experiment right. To Phil's credit, he said, "Let's do this the way it would be done to people. Let's adjuvant it," which means you add a second component which makes it more immunogenic, just like it would be for people. Up until that point, we were using Freund's or incomplete Freund's which just isn't used in people. It's a horrendous immunostimulatory compound. It's basically extract of tuberculosis. It's bad stuff. You can't use it in people, but we did it [in guinea pigs] because we wanted a raging immune response. We said, "We're going to do this just like people so we're going to use alum." Alum is used in people.

By this point Tim Gregory was involved. He was helping us purify the protein. He knew about formulations and stuff. So we adjuvanted it in alum. We vaccinated the guinea pigs just like people—three boosts, checked their antibody titers, and after the third boost they had a very high titer of neutralizing antibodies. We had a control group and a vaccinated group. I went up there with my virus and squirted them in. We're waiting. Four days later we go up there, unbelievable! Almost totally protected the vaccinated guinea pigs. Two, three years of work. Boom, there it was! Just unbelievable. The vaccinated guinea pigs maybe had a couple of tiny little lesions, whereas the unvaccinated guinea pigs were dead. We protected these animals from a horrendous disease. It was just an incredible moment. I'll never forget it. This is what it's all about. This has got to be the greatest thing. You can take a gene and show in an animal that it might work in people—this is the greatest. I would have never done this in academics.

Hughes: Follow that thought through a little bit more.

Lasky: Well, academics were really never an option for me, as we talked about earlier. But I thought, I am really glad I am here. They let me do it, and I could do it here so fast. I had Art's plasmids; they let me buy the virus; they let me buy the guinea pigs; they didn't stop me at any point, except this safety issue.

Hughes: You also had the money. Think of a molecular biologist putting in a grant to NIH—to make a vaccine.

Lasky: I know what would have happened. Bernard Roizman would have been on the study section. He would have done the same thing to me. The single greatest thing about Genentech, which really was probably mostly Herb [Boyer]'s input, was, let these scientists do what they want to do. If they're good, they'll come up with stuff. Let them publish it because that's the reward. That was the brilliant thing that Herb did. By far, no other company did that like we did. That and hiring Goeddel is what made Genentech. I'm serious. Of course, Goeddel would have never come if it hadn't been that circumstance. It just was elation. What was even better in a sense was we sent this paper to *Science* without Bernard Roizman, and it got in instantly. As soon as that paper came out, I knew what scientific fame was. It was newspapers all over the place. Interviews on television. My mother sent me some stuff from LA. "Here, you're in the newspaper." I showed these videos of me on TV to a girlfriend, and she's going whoa! That part of it is superficial, by the way, but it's fun. It was incredibly meaningless but fun. It was celebrity.

Hughes: How old were you?

Lasky: Thirty-three. Kid, total kid. This was the first time I really felt fame.

[Tape 3, Side B]

Lasky: First of all, it brought a lot of publicity. The stock went up five bucks in one day. Although it went up more when we announced the HIV results. It went up nine bucks, I think, in one day. It brought a lot of credibility but it's still never changed the collective mind of the upper management.

Hughes: They were worried mainly about liability?

Lasky: I think it was mostly liability and the fact that what Genentech really wanted to find were therapeutics for life-threatening diseases that they could use acutely and charge a lot of money for. That's the opposite of vaccines. Vaccines are preventative medicine which you can't charge much for, and you use a couple of times and that's it. That just went against the philosophy at the time. I can understand that.

Hughes: Growth hormone, of course, is not—

Lasky: Well, it's a chronic-use drug. This was tPA days, okay? While we're doing this, tPA is going on. TPA overshadows everything. Everything. Now, in large part that's because of the perception that tPA is going to be used in every myocardial infarction. Dave's incredible ego and Bob's willingness to listen to Dave over everyone else. So there's a lot of that going on. Our little herpes thing isn't going to compete with that. Not even close.

Hughes: What part, other than driving it, is Goeddel having in tPA?

Lasky: Goeddel's driving it. Once it was cloned, Dave wasn't that involved with it. No, it was more Art and the mammalian cell culture and getting it expressed, getting that to work. It was a development project. But it was Dave's project. Dave wanted the credit for it. Dave wanted to have all the drugs come out of his lab. That's how it was. Here are these little punks. They're nobodies. They came up with this [herpes] thing. Clearly AIDS was worse. It rubbed people the wrong way. How come these guys are on television? How come there are all these newspaper articles? How come they got a *Science* paper? "I could have done that." I heard that a million times. Well, why didn't you? [laughter] The devil's in the details, as Vishva Dixit always says.

Hughes: Do you think this internal competition was worse than it would have been in an academic department?

Lasky: No, the internal competition was fine. They had a bunch of ambitious, egotistical—they wanted fame, they wanted money, they wanted papers. They wanted everything. Everybody wanted everything. That sounds bad, but it's very healthy. It drove people. I wanted to be like Dave and Art and that drove me big time. They had more money than me; I wanted more money. They had more *Science* papers than me; I wanted more papers. It drove me big time, and it was fine. I mean, maybe it wasn't so healthy, but that's how the science world works. Competition is huge.

Hughes: In comparing academia to that early atmosphere at Genentech, you don't see too many differences?

Lasky: Academia didn't have the money component, clearly. Much later it did, but in those days zero. In fact, people got trashed because of the money part. I think in academia there was competition. But remember, in academia it's more little fiefdoms, right? In Genentech, we were all working for the company. I wanted my drug to help the company. The way I ultimately helped the company was very weird, I thought. In hindsight, the way I made a lot of money for Genentech was very bizarre but made sense because of the way I was, which we'll talk about again.

Hughes: You are thinking about the patents?

Lasky: Yes, the patents. There was all this drive to do this. I think the competition in academia was huge, too. I don't think it was any different.

Hughes: I've gotten the impression that at Genentech in the beginning there was a lot of, okay, to get this project going, we've all got to cooperate. If somebody can't do something, then somebody else steps in. By the time you come in 1982 it sounds as though things were getting partitioned off.

Lasky: Exactly. There were different departments. The reason insulin and growth hormone were that way was, first of all, Genentech was much smaller. Second of all, the concept needed to be proven that you could make a human pharmaceutical in a microorganism. Genentech was going to prove that. The company was very small, and so everybody had to work to prove that. Once that was proven, then you could say, well, now we can try lots of different things. We can try vaccines, we can try interferons, we can try tPA, we can try factor VIII. Then it got much more diffused. So they wanted more shots on goal. Then it in fact became more competitive. Who was going to come up with the next big thing? So yes, it definitely did change. It changed for the better because the competition was good. It was in fact the right idea to try and do this with other drugs. As many as possible.

What happened with herpes, though, was that they didn't want to develop it even though we had basically shown this had a very good chance of being a vaccine. In fact, they didn't want to develop hepatitis [B vaccine], which already was known to be something you could make money from. In fact, they sold it to SmithKline.

Hughes: Genentech could have developed the vaccine at that point?

Lasky: They didn't have that kind of development capacity. No, they couldn't have done it, I don't think. In hindsight, would they have been better off developing hepatitis rather than tPA? Absolutely. Hepatitis is a multi-billion-dollar drug. There was a big unknown about how useful tPA would be. We didn't know how useful hepatitis would be. In those days there was nothing known about any of that stuff. They took their chances. Same thing happened with factor VIII. Factor VIII was really the greatest cloning project done until that time, and Genentech sold it for really not much money because of various reasons which I am not totally sure of. In hindsight, that was a big mistake. That's a $400, $500 million drug.

Hughes: Why did Genentech undersell the herpes vaccine?

Lasky: I don't think anybody knew. I think they were trying to get rid of it.

Hughes: How did you feel?

Lasky: Well, by that point, HIV had arrived. I was onto the next big thing. I thought this was a dumb move, but I learned a lot. My confidence level went up. I showed these guys I was good. We got a lot of good papers.

Hughes: You weren't going to have much to do with developing the vaccine.

Lasky: I was not interested in participating in development at all. I wanted to move onto the next big thing scientifically. I would have advised them, but, no, it became a development project. In fact, SmithKline took the exact same protein we made and put it in the clinic and it's working. That's fine. Genentech will get some kind of royalty payment from it.

Hughes: You have the satisfaction of knowing that your vaccine is now being used.

Lasky: I was looking in the *New England Journal* [*of Medicine*] on the web. There was this announcement; GlaxoSmithKline makes this announcement: herpes vaccine 70 percent efficacious in women. I thought, God, I wonder if that's my vaccine? So I got the *New England Journal,* and it looked like it was our vaccine but I wasn't sure until I called the lead author, Larry Stansbury. I said, "Larry, what vaccine did they use?" He said, "That's your vaccine. It's the same exact thing, the thing you guys developed. And now it looks like it's working." So, seventeen years later, it worked. What more can you ask? My daughters will all be too old, but someday lots of little daughters will get this vaccine, and it will stop them from getting a very annoying disease.

Hughes: Now, that might be something that would be a different from the traditional view of what happens in academia where it's less common for somebody to be able to say, "Somebody's using the vaccine that I made."

Lasky: I think there are cases of it but it's rare, I agree. It's much more common in industry.

Hughes: And you like that part?

Lasky: Sure. Everybody wants to have something to do with developing a human pharmaceutical when they're in the biotech industry. The problem is 99.9 percent of people don't. Things mostly don't work. It could take decades to figure if they do work.

Hughes: How do people deal with that?

Lasky: I think the way you deal with it is you just say my probabilities are low, and if it works I'm very lucky. And you just do it.

Hughes: In academia you can persuade yourself that what you're trying to do is to add a little to fundamental knowledge. But you don't have to come up with a tangible product.

Lasky: In fact, that was one of the challenges at Genentech, which I thought was really great. It's actually much harder to be at Genentech than to be a professor at Harvard because not only were you expected to do extremely interesting science, you were also expected to do that science in the context of making a product. That is a challenge. That was really fun and interesting. Now, many people just blew that off and said I'm going to do whatever I want. But every project I worked on there I tried to find some kind of interface with the product. That was my goal, yet publish papers in *Cell*, in great journals at the same time. That was a challenge. It was difficult but I liked that part of it because really, if you're going to do science, why not try and make something useful. Even the adhesion stuff, that we'll talk about later, didn't come up with a drug but came up with patents which were used by other people to make drugs that hundreds of thousands of people take. I can't say it's my drug, but I can say they use it the way I designed it. That's my patent, which is also very satisfying. I like that part of it a lot.

Hughes: The next step is AIDS, right?

Lasky: The other thing that the herpes gave me was confidence that this approach could work on other viruses. In 1984-1985, herpes was winding down. This was successful. What do we do now? One of the great things about Genentech is that we have lots of visitors. We have lots of people coming to tell us stuff. In comes a guy I've never heard of, Don Francis. He is at the CDC [Centers for Disease Control]. I'm reading the newspaper. There's this thing going on where these gay guys are dying like flies. It's really weird. They can't figure out what's going on. Is it drugs? Is it a virus? Is it a bacterium? What's going on here? Nobody knew. All they knew was these young guys were rotting away. They had these terrible immunodeficiencies. They were calling it immunodeficiency syndrome. This guy Francis, who was well connected, he knew a lot of people looking on this disease, walks in, and he shows this electron micrograph of these T-cells. I think he got them from [Robert] Gallo. He says, "Looks at this. This may be what's causing AIDS." I say, "What is that thing?" He says that's a retrovirus. I kind of knew about retroviruses because recently the Nobel Prize had been awarded for reverse transcriptase and oncogenes. I was interested in oncogenes. Art's bosses, Mike Bishop and Harold Varmus, got the Nobel Prize because they discovered these retroviruses that carry oncogenes. Do you really think that's what's causing it? He said, "Maybe, nobody really knows." Of course, it didn't happen very rapidly, but it was proven that that was what was causing it. I thought this could be the next black plague. If the gay people have it, maybe we're going to get it next. What's going to happen? This could be the biggest disaster. We don't know what the hell to do here.

I also thought we're good at making vaccines. We made a vaccine for one of the hardest viruses ever, herpes. So let's think about making a vaccine against this thing. To make a vaccine of course, you need to have the virus, and you need to have its genes and all that stuff. How do we get that? As soon as the virus was announced, they wanted to make a diagnostic for it. A lot of non-homosexuals and people that got factor VIII got the virus in fact from blood transfusions or blood products. So they immediately wanted to test the entire blood supply and figure out whether there were antibodies against this virus. Well, they sort of made a diagnostic using the virus as the antigen. Then they looked for antibodies against it. Then they thought, well, maybe it might be much more convenient to do it by recombinant DNA. This stuff seems to be working. Why don't we try that?

They [NIH] awarded five different diagnostic awards which meant you could get ahold of the virus. Genentech got one of the awards to make a recombinant HIV diagnostic, with Baxter Travenol. We weren't a diagnostics company by any means. Sometimes we talked about doing that but we thought, AIDS is the next plague, and we have to help out, so let's make a diagnostic. So we get the virus, and this virus was different from herpes because herpes is a DNA virus, so it's easy to get the DNA and clone the genes. But HIV is an RNA virus. I was not an expert at cloning stuff from RNA. Probably the best cloner on earth other than Goeddel was a guy named Dan Capon. Because I was in the vaccine department as luck would have it, we were going to be guys that make this diagnostic. At that point we had morphed into the diagnostic department, if I remember right. All this time Berman is still working on herpes and playing around with doing some cell biology. I'm looking for something to do and along this comes. I knew Dan was a difficult guy. My best friend Richard Lawn hated him. They cloned factor VIII together, and it was just like horrendous. They hated each other's guts. Dan was very difficult to deal with. I thought, we'll clone this thing, and I'll take the genes, and we'll do our thing with them. Dan can do whatever he wants.

Hughes: Where was Baxter Travenol getting the virus?

Lasky: Gallo. At that point everybody thought Gallo had discovered it, and the French were nobody. [Margaret] Heckler made her famous, ludicrously idiotic announcement and also said, "We'll have a vaccine in two years." Gallo was the king. He probably had a glass over the ticket to Stockholm in his office: Break in case of Nobel. [laughter] He was on top of the world.

So we got ahold of this thing. Then Dan and I started to work on the cloning together, but that rapidly degenerated. First of all, Dan didn't like me being involved. He wanted to control the whole thing. We already have said several times, I don't like to be controlled. It basically degenerated. Fortunately, it degenerated very quickly, and I didn't hold it against Dan. I just said I wanted the genes however you can get them. This research was actually done in a P3-like facility at Genentech, so we had to do this in a room that was protected from the rest of the company because there were still issues about cloning pathogens.

Hughes: The facility pre-existed the AIDS work?

Lasky: Yes. I'm not sure why we had it. It was kind of a hokey set-up. I remember that wasn't really a real facility. But we did everything there just to keep everything separate.

To make a long story short, Dan and this very smart postdoc of his named Mark Muesing cloned this thing very fast, got a bunch of different clones, sequenced them, got the sequence, got all the splicing. They did this very quickly. They submitted a paper to *Nature* which they very nicely put my name on which I appreciate greatly even though I had almost nothing to do with it.

Then basically the world exploded because there were four papers that came out virtually simultaneously, describing the molecular description of HIV. This was huge stuff. Within a very short time—it's like SARS, actually—from when the virus was isolated the entire structure of the genetic material of the virus was described. One came from Chiron, one came from [Luc] Montagnier—it actually was done by another guy,

not Montagnier; he had nothing to do with it—Capon/Genentech, and Gallo. This was very controversial because it turned out that the virus that Chiron had was clearly different from the virus Genentech, Gallo, and Montagnier had. There was a big controversy about where did Gallo actually get the virus. It turned out from the sequence of the viral genomes you can clearly see that the Genentech, Gallo, Montagnier viruses were virtually identical, whereas the Chiron virus was completely different. This was when Gallo's world started to fall apart. People then started saying, "Well, why are they so similar? Gallo we know maybe got the Montagnier virus. The Genentech sequence is Gallo's virus. They're identical. Sure looks like Gallo's virus is really the Montagnier virus and Chiron's is different." Of course, subsequently, that's exactly what was found. That was a sad situation for Gallo but great for us because now we had the ability to make an HIV vaccine, we thought.

So simultaneously we did projects on viral genes in bacteria for diagnostics, and there's a very nice *PNAS* paper that I published—virtually the first one that showed you could actually diagnose AIDS with recombinant protein. A few weeks ago we got the patent for this. If anybody uses this, they'll have to license this from Genentech. I believe most of the diagnostics is done with recombinant proteins. But we weren't so interested in that. What we were really interested in was the vaccine. Now this turned out to be a horrendously difficult thing to do. So gD [glycoprotein D], as you remember, was fairly easy to express. I just hooked it up in a few different ways, and it worked very well. The viral envelope of HIV turned out to be a much more complicated protein. First of all, it was much bigger. Second of all, it had much more carbohydrate on it. It was half carbohydrate. Third, it was a dimeric protein, which was cleaved and it bound to another protein, so there was an assembly issue. What we wanted to do was the same trick. We wanted to make the gp120 so that it was secreted from the cell so it was easy to purify. But the second component, did it require the presence of that to get folded up right? We really didn't know anything. So I killed myself to do this. I remember lying on the floor, passing out, getting sick. It was really hard to do. A real challenge. But of course, the end point was so worthwhile I just wouldn't give up.

Hughes: Was the competition also on your mind?

Lasky: Yes, of course. My little lab at Genentech is doing this. We know Gallo and Chiron and Montagnier and everybody else is doing this. But of course, we did have mammalian cell expression, and nobody else did. That was our huge hook. That was again Art's huge contribution to this project, as with others. We were able to do it, and nobody else could do it. Finally, I thought of a trick, which was to take the front end of the herpes virus gD and hook it to the rest of the AIDS virus and use that front end of the herpes virus gD as kind of a hook to get it expressed and to purify it. Once I did that, it worked. It was incredible. We could make it in mammalian cells. It was beautiful. Not only could we make it, we could use this little hook to purify it because we had a monoclonal antibody against this little hook region. So in a very short time we were able to make milligrams of gp120. So we said, "Well, we'll do the same thing we did with herpes." Along comes Berman, formulates it, injects it into a bunch of different animals—rabbits, guinea pigs, all this. Now, we had a bigger challenge here because we didn't have an AIDS-neutralizing assay at Genentech. In fact, very few people had an assay where you could look at the effect of polyclonal antibodies on the infectivity of HIV.

This guy Jerry Groopman, who was an old friend of mine from Genetics Institute days and UCLA days, was a big guy in AIDS at that time. He had the neutralization assay. So I called him up and said, "Jerry, I think we might be making an AIDS vaccine here. Would you like to help us out?" He said, "Yeah, sure." He sent me the serum. We arranged the whole thing. Berman sent him a bunch of sera, all blinded. It was double-blinded. It was done with random numbers. I remember Phil had this random number book on his lab bench to generate numbers, which I thought was kind of funny. There was no way you'd have any investigator bias. Sent the sera to Groopman, and Groopman did his assay.

I remember I'm sitting in Phil's room. Phil's on the phone with Groopman, and I'm watching Phil. He just gets this gigantic—he's looking at the numbers—this gigantic grin on his face, and it worked. I thought, gee, we might make an AIDS vacccine. [laughter]

Hughes: Meaning there's antigenicity—

Lasky: We had antibodies that neutralized the AIDS virus. I thought, we might do this. I really remember thinking at the time, we might make a vaccine for this. This shows you could do it. So we write up a *Science* paper, send it off, boom. I'm first author, Phil's last author. So the *Science* paper's percolating; we're waiting to hear if it would get accepted; we knew it would. But at the same time, the first annual AIDS meeting is happening, and of course it's happening in Paris because that is where Montagnier is, and that is where HIV was discovered. So they have a "vaccine" session. Of course, nobody knew squat [about] what was going on and sent in an abstract. I get chosen to give a talk. Now, this was a fairly big deal because remember, from the Bernard Roizman days, this guy wouldn't even submit my paper. Now, we submit an abstract with minimal information suggesting that we'd done it. Everybody wanted to show that you could make neutralizing antibodies at gp120 because that's step one of a thousand steps to make an AIDS vaccine. There's a buzz, Genentech's done it. And this abstract—what's going on?

Beginning of that year, I met my future wife, Melissa Loui Lasky. We were dating, and she was actually a computer chemist. When she met me, I'd just come back from an all-night party with these people from the San Francisco Ballet Company who were all my friends. I used to hang out with ballet people a lot. I was all disheveled, and I had on these hip clothes, and I had this short, buzzy haircut. Our dogs introduced us in a park. She said, "What do you do?" And I said, "I'm a scientist." And she said," Yeah, right. What's your name?" She immediately searched me, okay? She found I indeed had a bunch of publications, so then she thought I was okay. I wasn't a slime-ball guy. So we started to date. I get invited to this meeting. I say, "You want to go to Paris? I've got to give this talk in Paris." I didn't know what was going to happen. I was just going to give a talk. I had given lots of talks and nothing happened. She said, "Yes, let's go."

[Tape 4, Side A]

Lasky: Tim Gregory was there because we had all done this together, and we were a team. I was the first author, and I did the cloning, and I got it expressed, so I was the guy that was going to give the talk. So we go into this vaccine session. The first thing that struck me was there were like five hundred in this room. It's packed. The second thing that

struck me is a lot of them are reporters. I had been through this with herpes but not like this. You know, guys with cameras and boom mikes and all kinds of stuff.

Hughes: They'd seen your abstract?

Lasky: There were rumors that we had done this. Remember, that Heckler said, "We're going to have a vaccine in two years." There were rumors that this may be it. People were dumbly impatient and naïve at this time. This was the black plague. Everybody wanted a vaccine. It was incredibly naïve, but that was the thinking. There were a bunch of talks before mine. I think mine was actually the last talk, if I remember right. I'll never forget one guy, Bill Haseltine. He was not a nice person by any means. He heard this rumor, and he actually called me several times in my lab. "What's going on?" I wouldn't tell him. "Does it neutralize the virus?" I said, "Bill, come on, I'm working. I'm not going to tell anything." He was really pumping me. And Gallo called a few times. Bill got up and said, "Well, you may hear a vaccine story later, but don't believe it. It doesn't mean that much." I'm looking over at Phil, and we're just shaking our heads. What an asshole. He doesn't have to say this stuff. Just trying to steal thunder is what he was trying to do.

Then the guy before me gets up and talks. Then I'm seeing this buzz. Some reporter was in front of me, and he said, "Is that him?" And the guy said, "No, he's next." I'm going, oh God, I think I know what's coming here. So the guy finishes his talk, polite applause. I get up—no tie, blue jeans, the sleeves are rolled up. I'm a total nerd. My hair's the usual disheveled. I'm not like a smooth, slimy-talking guy. I give this talk and basically people went ballistic. I mean, people went absolutely ballistic. I walked out of the room, and I was mobbed by reporters. Microphones in my face. Montagnier comes up and says, "Congratulations." I look over; Haseltine has slunk away in the corner. I'm sure he was getting ready to take a Prozac. Phil, please come over, help me. It truly was nuts. It was Warholian celebrity for fifteen minutes. I didn't want to be committed. "Is this a vaccine?" "Maybe." "Is this going to work in people?" I said, "Maybe.

Then there were other interviews. All over the world I'm in the newspaper. In France, I'm in the newspaper, in Africa, everywhere. I get clips. People send them to me. I have a scrapbook full of this stuff. It's just insane. There's a picture of me, Phil, and Groopman sitting at a café together, a gigantic picture of us in one of the Parisian newspapers. It was just insane. So that was the absolute height of insane fame scientifically. If the vaccine had ultimately worked, that would have beat it. [laughter] When I got back to Genentech, the stock went up nine dollars in one day based on this one single talk. I believe it was something like that. Second of all, I get back to Genentech, I look at my desk and there's a stack of newspaper articles there. People are pissed. Art's pissed. Capon's pissed. They won't remember it this way, but I remember Art saying, "I'm underwhelmed," or something, and Capon is, "I could have done that." Incredible. "Who is this guy? [laughter] How come he did this?" I guess I did it because it was incredibly hot, and I thought we could do it, and I was ambitious. That's why I did it. They didn't do it. There's no doubt they could have done it, but they didn't. They did other great things, but they didn't do this.

We're now sixteen years after this event; making an AIDS vaccine has been impossible. The utter euphoria of the time has degenerated into utter depression. I got out of the field, fortunately, in time. But I did do one other thing, which was to localize the gp120

binding site for CD4 binding because I thought if there's a way to do this, we could do this. This was something that Capon and I did. It was the first real hardcore scientific thing I did at Genentech in that it was a very exciting basic research result. By mutagenesis and by a lot of other technology and antibody binding and peptides and all kinds of stuff, we discovered the region that AIDS used to stick to the cell. I was kind of tired of doing only product-oriented stuff. I wanted to do a real hardcore—I didn't have a *Cell* paper yet, and that was bad. You needed a *Cell* paper, at least one, and I didn't have any. I wanted to do something that gets a *Cell* paper. I had *Science* and *Nature* papers. Dave and Art had all these *Cell* papers.

Hughes: *Cell* doesn't accept applied science?

Lasky: No, they want more basic research. They want big discoveries that are earth-shattering, that are really important. That's what *Cell* goes for. So I thought if we could figure out the binding site, we could get a *Cell* paper. So that was a lot of work, a great collaboration with lots of different people. At the end of the day, we figured it out. It got in *Cell* pretty fast. A scientist I personally think is the smartest scientist of anyone is David Baltimore. I had met Baltimore a few times. He came to my herpes talks, and he came to my AIDS talks. I think he thought I was okay but not that great. I remember when I gave this talk on this binding site, *Nature* wrote a "News and Views" [article] about the discovery. *Nature* sometimes wrote little stories about things that appeared in *Nature*. The quote from Baltimore was, "This is one of the most impressive displays of molecular biology I've seen applied to a virus ever." And I thought, God, that is great. That is better than the reporters. [laughter] They called it the Lasky site for a while, and it was really a big deal. I thought this basic research stuff is also pretty great. The point was we wanted to discover that region to try and direct the vaccine against that site because that site should be the same in all different viruses. But even that site is divergent in many different viruses. So that's been useful but not critical information.

Hughes: When did it begin to dawn on you and others that inducing an antibody response was not going to be sufficient for producing an effective vaccine?

Lasky: Very early. That is when Phil and I departed company because Phil took a reductionist approach to everything, and I took a complexity approach. Phil didn't like complexity. He was a reductionist.

Hughes: Here you are coming out of molecular biology, and you're basically a cloner, although I realize other things have happened in between. Biology means knowing something about immunology.

Lasky: Right. It's very interesting, the term cloner. There were certain people at Genentech who were more "biologists." Basically, they were mediocre scientists. They would always call us molecular biologists cloners because cloning was extremely powerful, and this frightened them because it allowed people who were "not biologists" to make major discoveries. Certainly the tag cloner was applied to me and Lawn and lots of people. It actually was baloney. If you're smart enough to be a molecular biologist, you're smart enough to do any biology, for the most part. Now, there were some exceptions to that. We really were pretty bright guys, besides just sticking DNA together. I knew a hell of a lot about immunology, and I read. One of the things I did probably I have to say better than anybody at Genentech, even Art and Dave would

admit that, was to read and retain stuff. I read a huge amount of stuff in lots of different fields so I knew way more than most of these guys did. So that allowed me to make more intelligent decisions. The next project I worked on was a hardcore immunology project because I'd read all the papers on this stuff. I really was much more aware of a lot of things because I like to read. That's the bottom line; I like to read science. It's a great way to figure out what is going on.

Hughes: What were you saying to yourself when you found a way of getting a pronounced antigen response from your vaccine?

Lasky: At first, I thought maybe an antibody response would be enough because it's enough for certain viruses. There was a little bit of delusion on my part because I was high on the possibility that I might have made the AIDS vaccine, okay? But my problem is, I'm a negative guy, and I tend to err on the negative side. After looking at how variable the virus is, after publishing some papers of our own which showed that neutralizing antibodies against one strain didn't touch other strains, I started to feel the foundation getting a little shaky. Within probably a year or so, by 1988, when I had figured out that the gp120 CD4 binding site isn't that good, the foundation was getting even shakier. To a lot of people in the HIV world, the foundation also was getting shaky. I actually wrote a big review about HIV vaccines. That was the last thing I wrote on HIV, which was very negative. It was in the *CRC Reviews,* and I was a single-author reviewer. I was the only guy. I wrote the whole thing myself. It was a pretty negative review. I basically was out of the field. I said [to myself], this is going to be too hard. I like too many other things. I want to find something new to work on. This is just not going to work. I don't want to spend my entire life making it work. I'm a noble guy but I'm not that noble. I am not going to sacrifice my career to make this work. The decision in hindsight was excellent because I don't think my being in it would have made a whit of difference. I think there still wouldn't be an AIDS vaccine even if I killed myself to do it. It's just maybe too hard to do, it may be impossible to do.

Hughes: You think?

Lasky: It's possible. Now, as the years pass, things change. We may come up with new discoveries, about the immune system, about viruses. But as of today, I think it's extremely unlikely.

Hughes: [Jonas] Salk kept pushing the killed vaccine idea.

Lasky: I'm glad you reminded me of Salk. I got the Salk [polio] vaccine. I knew who Salk was. He had come to Genentech a few times. He would give a talk. The room would be packed. The talk would be horrendously bad. But he is a great man. He did a great thing. I wanted to meet him; I wanted to talk to him. So after the big announcements and all this, he would call me at my house. One of my great regrets in life is that I never got an autographed picture of him with me. I wouldn't say he was my buddy, but we talked often. I would go down to the Salk Institute, and we would sit in his palatial office overlooking La Jolla, and we would talk about AIDS vaccines. Did I respect him? Absolutely not. Zero. Scientifically terrible.

Hughes: Why?

Lasky: Because he was in the fifties. The idea of chopping up, dumping a virus into formulin. Come on, this is the molecular biology era.

Hughes: He had a company.

Lasky: He had a company, Immune Response. That's what they were doing. Now, why did that [method] work with polio? One, polio is essentially a crystal, so a single antibody binding to it kills the whole virus. So it's easy to kill polio. Two, polio is very hard to get in that it enters orally but it doesn't really cause any problems until it gets to the central nervous system. That's a long way to go, so there's plenty of time for the immune system to kill it. HIV is an envelope virus, which is much harder to kill because it's floating in an envelope environment, and two, HIV infects the cell it first sees. It immediately inserts its DNA into it, and you've got it. So Salk's thinking was naïve, simplistic, wrong, et cetera. But he was a great man, and I'm glad I met him. I'm glad I talked to him. His input to the HIV thing was zero.

Hughes: What Salk did with his polio vaccine would be considered a cell-mediated approach, right?

Lasky: Sort of but not really. What he was doing was quite dangerous. There was viral RNA there. You could have gotten the infection from it.

Hughes: My brother did get the infection from it.

Lasky: Well, there you go. That was bad. Second, to really get a cell-mediated response, it's much more difficult than just tossing in the whole gemisch. There are very sophisticated ways to do this now. There are sophisticated adjuvants you can use. There are sophisticated antigen presentation methods you can use. I mean, the days of tossing in a gemisch are long gone. So maybe he was kind of thinking along those lines. Of course, the object of getting a cell-mediated response is in fact correct; we do want that with HIV. That's why the vaccine trial probably failed—because they had zero cell-mediated immunity. The way Salk was doing it was 1950s technology.

Hughes: You see what I'm saying? If you could reject Salk because he's an old-fashioned scientist, you could then also dismiss, at least until the evidence became too hard to miss, that you didn't want his way of approaching a vaccine at all. You've got this new technology that seemed to be much safer and had a short but nonetheless dramatic record—vaccines that work have been produced using it.

Lasky: Right. I think that's what I was thinking, but I think the best thing Salk did was have a kind of galvanizing effect, the Great Man effect. I wanted to make him happy. My conversations with him were just more like a hero kind of a thing.

Hughes: It wasn't two scientists talking?

Lasky: No. He mostly wanted to know what I was doing. I think he was kind of gathering information. He utilized his greatness. People like that know people want to be with them. He's no dummy. He knows he could call anybody—Gallo, anybody. In spite of their opinions of his science, they would be more than pleased to talk to Jonas Salk. Look, he's one of the great figures of medicine in the [twentieth] century. How often do

you get to meet somebody like that? I've met a few. I've met Baltimore and Bishop and Varmus. They're better scientists; they've made major discoveries. But Jonas Salk is a household word. Everybody knows of him.

Hughes: Please comment on the 1994 meeting in which [the FDA] decided that the Chiron and the Genentech vaccines would not go forward into large clinical trials?

Lasky: I think that was the right decision. It's really quite amazing that these issues are still being discussed. I was with a guy yesterday who sits on an AIDS vaccine panel, and I said it must be very depressing to be on this panel—nothing is working. He said it is. But then he said what I thought was really wacky. "But the subset analysis of the VaxGen [trial]. Should we do a trial on blacks?" I said you must be joking. That subset analysis was not statistically significant. It makes no sense immunologically, if that's the case. The sample size was too small. NIH will never go for that. But in fact this was the same argument back in '94: "Well, you never know," and "It's the black plague." I find that to be counterproductive. Look, VaxGen's spent hundreds of millions of dollars and got zero. They didn't get a scientifically significant result. They just proved that what they had was ineffective. This cost a fortune. There were many, many, many people out there—me included, David Baltimore, guys who have been around the block—who said, "This will never work." I think the decision that was made was perfectly acceptable. Why put a lousy vaccine into the clinic? Wait until you have a reasonable chance of one working. You do what Merck's doing, which is doing a million experiments, trying a million different ways of inducing T-cell responses, B-cell responses. They're doing it right. That's what it's going to take. It's going to take the complex approach to solve this problem.

Hughes: There's enough stable in the virus that—?

Lasky: The core of the virus is conserved, and there are internal antigens which the T-cell response would recognize which have a chance of being conserved enough. That's why you want both arms. There may be regions of gp120 that are conserved enough where if you can get a good robust response specifically to that region, it might work. If I wanted to go back into academics right now, I would toy with the idea of playing with HIV again.

Hughes: Would you?

Lasky: Yes, there's been a lot of water under the bridge. There is a lot of new stuff that we know. There are new ways to approach this stuff. There are more people to collaborate with that are smart and savvy. I think times have changed. I'm not saying it'd be the only project I'd work on. It would be one project in my academic lab.

Hughes: What did you think of Jon Cohen's argument that the national organization of the AIDS vaccine effort left a lot to be desired?[1]

Lasky: People want to restart this Manhattan Project thing. That's been the analogy. Well, it's not really the Manhattan Project for a couple of reasons. One, it's way easier to build an

1. Jon Cohen, *Shots in the Dark: The Wayward Search for an AIDS Vaccine*, New York: W.W. Norton, 2001.

atomic bomb than make an AIDS vaccine. Building an atomic bomb is isolating enough plutonium or U^{235} to do it. Other than that, it's not that hard. Second, when the Manhattan Project was going on, there was a foreseeable enemy out there which we thought was doing the same thing. Turns out the Germans weren't, but we were convinced they were. There was a time issue here. Either we do it first or they do it first. If they do it first, we lose. Third, because it was wartime, you were able to take people out of their private lives and put them in one place, Los Alamos. I hope you've read this book by Rick Rhodes.

Hughes: Yes.

Lasky: It's the greatest book about that whole thing. So they were able to put these guys, like [Richard] Feynman, [Hans] Bethe, just genius guys, in one place, and they just nerded out and did it.

I don't see it happening with an AIDS vaccine. I think it's much more difficult to do it now. It's hard to coordinate people, and people have their own agendas, and they have their own labs, and they have their own project they're working on. I actually would like to help in some way since I was the first guy to make anything that looked like it. It's logistically impossible to do it. I just can't see it happening. What do you do? Tell some famous guy who's got a full Howard Hughes professorship at some university to drop what he's doing and move someplace and make an AIDS vaccine? Let's face it. AIDS is not an American disease; it's not a European disease. To tell you the truth, what I like the most about the idea of developing an AIDS vaccine is saving the third world. Those people are misery incarnate. Anything you could do to help them would be great. To me, the most exciting thing about making a vaccine would be giving it to people in Africa. Just give it away.

Hughes: Companies, including Genentech, have been criticized for working with the clad or family of the virus which was not prevalent in developing countries. So even if they got a vaccine, there was a big question whether it would be effective there.

Lasky: Yes. I think that was really a selfish economic decision. Even if there were a perfectly effective AIDS vaccine in the United States, how many people do you think would really take it? What are our chances of getting AIDS? Almost nothing. Compared to hepatitis C or herpes or any of these things, it's hard to get the disease if you don't have a certain lifestyle. It's really not an important disease in the United States. That's another problem with developing it. Do you really want to put hundreds of millions of dollars into developing a vaccine to be used by people who spend one dollar a month on health care? But if you talk about doing a great thing for society with your science, I think there isn't much that defeats that.

Hughes: A company, looking at it very crassly, would do it for the glory and the fame. Imagine what an AIDS vaccine would do for Genentech.

Lasky: Whoever does it will be immortal. That was part of the appeal. Cancer is even a little easier, as hard as that is, because there is a lot more known about that.

Hughes: Adhesion molecules?

Lasky: Right. Adhesion molecules were interesting because they was really far from anything I'd ever done before.

[Tape 4, Side B]

Lasky: My confidence level was definitely higher, but I really wanted to get out of HIV. By that point my lab had gotten fairly large. My lab was never really big. There were never more than six people. I always had good people. I always had good postdocs. There was a guy in my lab named Scott Stachel. He was my first scientist there working for me. He was a very smart guy, odd person but very smart. We were tossing around for a project, and we started to read papers by this guy Steve Rosen at UCSF. They were very interesting papers because first of all, they involved something important which is the immune system and how lymphocytes got from the circulation into the inflammatory site. What Steve discovered, which was completely novel, was that these lymphocytes stick to the blood vessel wall. But the way they stick is not by binding to a protein but it looked like they were binding to a carbohydrate. This seemed very interesting because it was completely novel. We thought maybe we should start looking more carefully at this.

Then we got scared because we saw that this guy Irv Weissman was working on the same thing. Irv is and was one of the most brilliant, powerful scientists in the world. We thought, well, we'd like to start working on this, but this guy is going to kick our butts. Stachel said, "Oh, God, he'll kill us." I said, "Well, Scott, it's likely we're much better molecular biologists than Irv. Let's see if we can clone the thing first and get something there." So how are we going to clone it? Well, the only way anybody cloned anything in those days for the most part was, you got the protein that you were interested in. Then you sequenced it with a machine called an amino-acid sequencer. Then you designed a piece of DNA from the genetic code. You did a reverse of the genetic code. Then you use that piece of DNA to fish it out of the library. That's how tPA was cloned and factor VIII and all this stuff.

So I thought, well, maybe this guy Rosen could help us out. So we called up Rosen, and again this is the greatness of Genentech. First of all, nobody told us to do this. Second of all, we could just talk to anybody, and they'd listen to us because we're from Genentech. Soon as they heard you were from Genentech, they'd want to talk to you. So I called up Steve and said, "You don't know me, but I've read your papers. I think they're very interesting. Do you think we should clone this thing?" He said, "Yeah, that will be interesting to see what it looks like." I said, "Well, we're going to need some protein. Can you purify it?" He said, " I've already purified 200 micrograms." I thought, this is incredible. I said, "Can we have it?" He said, "Yes, you can have it. I don't know what to do with it."

So we got this arrangement together. We did a license, and this was my first experience with licensing, and that was kind of a drag. But we finally got it done. Then the other great thing about Genentech was, downstairs we had this guy Bill Henzel. Bill was the greatest protein sequencer on Earth, bar none, no competition. The guy was a genius. There were a few geniuses at Genentech, people I would truly say are geniuses. They can do things that other people can't do. What they do would not be done unless they were there. That's my definition. I don't call myself that or Art or Dave because if Art

or Dave or me hadn't done our stuff, probably somebody else would have done it maybe later.

This guy Henzel really was pretty amazing. He made these machines. No matter how sensitive the machine was, he was dissatisfied. So first he was sequencing proteins at the micromolar level. That wasn't good enough. Then the hundreds of nanomolar. That wasn't good enough. He just kept pushing the envelope. He never was satisfied, this guy. Classic obsessive guy, and how can I make this better? So I said, "We've got Bill; we've got this protein. We're going to clone this sucker." So we take the protein down to Bill. Bill says, "Unless the N-terminus is blocked, this will be easy." There is a ton of protein. Two hundred micrograms is a lot of protein for a guy like Bill who is used to getting much less.

First week, we put it on the sequencer; come back on Monday. "Bill, where's the sequence?" "We had a power failure; it broke; your protein's history." I thought, God this isn't so easy, actually. [laughter] I went back to Steve. "Could we have some more protein?" "Sure." He gives us the protein. Next run, thirty-seven amino acids in a row. Unbelievable. Just perfect. No questionable sequences. Because of the nature of the genetic code, there are more codons for certain amino acids than for others. So you want amino acids with the fewest numbers of codons because that makes the complexity of your DNA probe much less.

There's a funny story of a guy at Genentech who designed a probe which had a million different sequences in it. Goeddel always razzed this guy about this. Methionine and tryptophan are the best because there is a single codon for those. Our [probe] had a lot of mets and tryps, so we were very happy about that. So ours was very simple. Dave Martin was our first VP of research. I was again not that interesting to Martin. Goeddel was everything. Martin knew where his bread was buttered. I'm going to Dave's house in a few weeks so I still talk to Dave Martin. So Martin didn't pay attention to us. After all we were working on vaccines. Who cares about those?

Martin got wind of what we were doing [on selectins]. He said, "This sounds kind of interesting. Maybe there's a product here. Maybe we could block inflammation." So he said, "Why don't you go try to collaborate with Irv Weissman? After all, he is a very powerful guy. You've got this sequence. Maybe he's got a library or something." What did I know? He was the VP. Weissman was a big guy. I thought, I'll go down and talk to Weissman. So I went down to Weissman. It was me and Scott and maybe somebody else went. I remember there was this room full of Weissman and all these postdocs and this one guy, Mark Siegel, who was the guy working on this for Weissman. "How do you do it? What are you guys working on?" "Well, we're working on cloning the homing receptor." (It was called the homing receptor or Mel 14.) Irv turns out not to consider anybody competition because he just thinks he'll beat everybody. That is the kind of guy he is. "Oh, isn't that nice," was kind of the answer. I said, "The other thing is, we have thirty-seven N-terminal amino acids." He lost it. "You can't work on it. I have a patent." I said, "Actually, we can work on it. There's nothing to stop us from working on it. Do you want to collaborate or not?"

I knew where it was going. Academics hated Genentech. They hated our guts. Genentech could get in a field overnight and blow people out of the water—just ruin people's careers. Goeddel or somebody could just go in and kill anybody because

nobody could clone like we could, and nobody could do sequencing of proteins or DNA [like we could]. Nobody could make oligos [like we could]. In the eighties, nobody could clone like Genentech. People hated us for that. They either liked us if they were doing it with us, but if they weren't, like Weissman, they just lost it.

So we went back. "Dave, this is a big mistake. We've awakened a sleeping tiger here." [laughter] So very quickly we designed the oligos, screened the library, saw the spot, pulled out the clone, sequenced it. I was having a baby at this time, my first kid. This was 1988. So Stachel got the first sequencing data and said, "This is really interesting. There's a carbohydrate binding into domain in here. This is totally new stuff. It's a brand new class of adhesion interactions. This is a major discovery." Rosen is going crazy because all the work he'd done is now confirmed by the cloners. He's thinking of where he's going to go with this, but of course we had to get the paper published for all this to happen. So we write up this paper very fast, minimal data.

In those days if you had a new sequence and some biology—like it was expressed; you could precipitate it with a monoclonal—you could get a paper in *Cell* or *Nature* or *Science*. So we sent the paper off to *Science*. The problem was Weissman was an editor of *Science.* Weissman came close to killing this guy Siegel, but Siegel finally got a clone. The way they got it was weird, though. We still to this day can't figure out how they got it because their sequence information was bad. They made other mistakes. Anyway, it's a long story. The paper was never retracted, and it should have been. They got it into *Science* a few weeks before we did. So Weissman's an editor. Weissman gets it in fast. *Science* sends me a letter saying this is really great, but you're too late. There's already a paper. It's in press, and it's too bad. So that's bad. What can we do quickly?

I hear through Rosen and a friend of mine, Brian Seed, that this isn't the only one of these proteins. It turns out there are two other ones. So not only is this a new kind of protein, it's a new family of proteins. You can't ask for better than that—overnight to discover a whole new family of adhesion molecules. Unheard of, okay? So I call Brian Seed. "Where are you guys sending this stuff to be published?" This really nice guy, Rod McKeever, had the other protein. There were three total. "We sent it to *Cell*; it's in press." I go, "Fuck!" First of all, I sent the paper out before getting permission from Genentech, which I got in trouble for, but it was Machiavellian. It was worth it. Second of all, I called up [Benjamin] Lewin. I either called him or wrote to him. I said, "This is the third one in this family of proteins. It is a major new class of adhesion molecules in the immune system. *Science* has the same thing." Well, Lewin hated *Science*, and *Science* hated Lewin.

Hughes: You knew this?

Lasky: Yes. Everybody knew it; it was common knowledge. Lewin thought, Jesus, not only could I beat *Science,* but I'll have all three in the same issue. So in less than one day the paper was accepted. I got a fax. Other guys that had *Cell* papers at Genentech just cracked up; they said, "This is the fastest ever acceptance of a *Cell* paper, and it was purely because of the circumstances." So this paper's accepted. I get a fax. "You're going to get the galleys tomorrow. You better send them back the next day because this is coming out in two weeks." This kind of stuff. It was just great.

The interesting thing about this is not only are we competing with Weissman but we thought we were competing with Goeddel on this. First of all, you never compete with Goeddel because you always lose, and I knew that. I'm thinking, I sure hope this is a different protein than what Goeddel is doing. Second of all, I don't want to piss Goeddel off, but I can't stop doing this. Goeddel had a big lab. People would come to Goeddel all the time with projects to clone. Goeddel would put a guy on it because Goeddel was a great cloner. No big deal. These papers come out and revolutionize the world. There were many people working on carbohydrates but nobody knew what they did. Nobody had a clue. Other than Rosen, along come these cloning guys who purely by DNA sequencing for the first time say carbohydrates are involved with trafficking various white cells to various parts of the body. This was a concept nobody had had before. Rosen was the first guy. Other than his first few papers, nobody got this. *Science* wrote a big "News and Views" [article] on it, showing all three family members. Just incredible excitement.

At the time, there was a lot of confusion about this protein that Gene Butcher, who was a Weissman collaborator and postdoc, was working on that Gene's protein was the human homologue of the protein we were thinking about. The protein we were looking at was a mouse protein. The protein Gene was looking at was a human protein. Pretty much everybody in the field thought they were the same protein. So Goeddel was doing this with Gene. We were having a little trouble cloning; our library was bad or something. Dave said, "Why don't you just wait? We'll get the human one, and then you could just use that as a probe and get the mouse one." I thought, shit, thanks a lot Dave. You're my buddy.

I also remember hearing this story. A Chinese guy was cloning for Goeddel. He was terrible. I remember hearing through the grapevine that he told this Chinese guy, "Well, you're competing with Lasky, and Lasky's never cloned anything important. You should be able to kill him." He's getting him all fired up, right? Anyway, they got a clone for theirs and we got a clone for ours. We did a hybridization experiment. The thing Goeddel was cloning was not remotely like what we were doing. In fact, when the sequence was finally done, they had some crummy paper. It was boring, just totally meaningless. I think Goeddel might have changed his mind about me when all that happened because from this one project I got two *Cell* papers, a *Nature* paper, two *Science* papers, and a bunch of other papers in *Journal of Cell Biology.* This was really a hot project. I think Goeddel was saying, "Well, maybe this guy is more than a vaccine guy."

Hughes: Why was Goeddel in it in the first place?

Lasky: It was one of Goeddel's many things. It was a minor thing for David. It was a major thing for me.

Hughes: The way you told it, I got the impression that this field at first was virtually unknown but became a hot field.

Lasky: Overnight, it became hot because, first of all, it looked totally new. Second of all, it looked like maybe because it recognizes the carbohydrate and carbohydrates are small, that a small-molecule inhibitor of inhibitor inflammation could be developed. That's a big deal.

Hughes: Anything more?

Lasky: Yes. Another big deal at Genentech is that the serendipity aspect of the place was huge. So one never knew where research would lead you. That's always true of research, and one never knew what was going to come out of what you were doing. That was actually one of the great things about scientific management, especially with somebody like me. David Botstein said this about me once because I was doing some weird stuff. David said, "Leave this guy alone. You never know what he's going to come up with." That really was a great part of that place. I'm not sure if it's like that anymore. Certainly, they let people follow their noses if they trusted those people. So if they thought you were a smart guy, they let you follow your nose.

This adhesion stuff was very interesting, but where is it going to go? Are we going to get drugs? Everybody was wondering, although it seemed we were going to get drugs because inflammation is important. Blocking it is important, and maybe that's what will come out of it. But we didn't know. In order to figure out how these worked, we had to look at what they bound to. Nobody knew how to do that because, remember, you have this protein but you don't know what's on the other side of the interaction. There's no real way to figure out. So you can make a monoclonal antibody to what's on the other side of the interaction, but that's a pain because you have to screen thousands of antibodies. You don't really have anything to induce the monoclonal production. It was crazy. So I thought about this, and Rosen and I were discussing it. Actually Steve thought he was going to solve this problem. He said, "I'll go on my way. We'll talk in a few months, and I'll think of a way to do this." I thought, okay.

At this time Capon, who was very good, nuts but good, was doing this CD4-IgG stuff. I looked at what he was doing, and basically the concept there was to use CD4-IgG to block viral infection. The way it worked was CD4-IgG was kind of like a monoclonal antibody because it bound to the gp120, and it inhibited the gp120's activity. Actually, we used the CD4-IgG in the previous AIDS work as a monoclonal antibody to immunoprecipitate gp120 mutants. So it's funny how it all comes around. I remembered the work we did with CD4-IgG, and I remembered it was kind of like a monoclonal antibody. Then my mind worked around that: Maybe we can hook up something else instead of CD4 and use it like a monoclonal antibody.

So Dan and I had lunch together, and I said, "What do you think of this idea? I want to figure out what this is binding to. I don't want to make monoclonals but maybe I could just use this thing like a monoclonal." Dan said, "I don't know, maybe it'll work. I'll give you the plasmid and try it." Again, one of the great conveniences was, Dan was there. Dan didn't necessarily like me a lot, but he was willing to help me because we all worked at one company. He said, "Hook it up here and do all this stuff and it'll work." I did what Dan told me and lo and behold, I got this protein whose front end was the homing receptor, the carbohydrate-recognition protein, and the back end was an antibody. When you look at this thing it really looks like something that can find what it binds to.

Interestingly, what's going on at the same time is Brian Seed, who is far smarter than I am is percolating these same ideas. He's coming up with this same kind of stuff but he's using a different protein. We're hearing rumors that Brian—Brian's a potent guy. I don't want to compete with him, but this is such a good idea. So how do we look at this

and find out if it works? Well, the first experiment we did was really pretty clever. The endothelial cells where this thing binds to—the cells bind to the endothelial cells, the T-cells, using this interaction. So why don't we use this chimeric protein—by that point it was called a chimera—and try to stain these endothelial cells like you would stain with a monoclonal antibody. The way it would work is this thing would bind to the endothelium, and you could visualize the thing it's binding to just like you could visualize it with an antibody.

Susan Watson, who was working for me, was an expert at this stuff. She did the experiment, and it worked. I call up Rosen, and I say, "We can find this thing now." He said, "What are you talking about?" I said, "Well, here's what I did, and he said, "Man, what a good idea!" So we started collaborating, and we find that we can actually purify proteins using this like a monoclonal antibody. We purify two different proteins and sequence them and clone them and discover a whole other class of adhesion molecules that these things bind to, using this technique. Now, this time Susan Watson's thinking about what she can do with this. She said maybe she could use it as an anti-inflammatory. So nobody was really getting this whole thing, although Goeddel did.

We published this paper in the *Journal of Cell Biology,* showing that you could use this chimeric protein as a probe for the ligand that it bound to. Goeddel read this paper and said, "It's too bad you published it in that journal"—because unless it was *Science, Nature*, or *Cell,* Goeddel didn't think it was that great—"it really is a good idea." I said, "Wait until you see what we do next because we're going to figure out what it binds to." What it bound to were mucins, which are long carbohydrate-presenting proteins. It turned out there were now four family members. In that period of time, Rosen and I discovered two completely new families of adhesion molecules, totally new. So the patent people are starting to think maybe this is useful stuff.

Then Watson does a very interesting experiment. If you inject mice in their gut with this junk called thioglycolate, you get this massive inflammatory response. Their gut becomes like pure pus. Watson said, "Maybe we could use this chimeric protein to block that. That will show two things. One, that this interaction is important for inflammation in vivo, but it will also suggest that this thing in itself might be a drug." She does this experiment, and it works incredibly well. She can block information with this chimera. We write a *Nature* paper, and it gets in immediately. That is the last thing I did that actually got in the newspapers. It got in the *Wall Street Journal*. It's this cute little article this friend of mine wrote. But it was a very interesting demonstration because it showed that these things might be drugs.

Then the patent people got real interested in this. I get a call from this woman named Ginger Draeger who is my favorite patent attorney. She is super smart, very conscientious, a great writer, understands science. She was my favorite one because I had a lot of dealings with patent attorneys. So she writes a claim I thought was amazing at the time, which was, "From these data we predict that any cell-surface protein attached to an antibody tail this way, can be made and used as a drug." I thought, you'll never get that. This is a single example, and how are you going to get that? Well, she got it. What you always want with patents are broad claims. This claim is beyond broad. Anyone that makes a drug by taking a cell-surface protein and attaching an IgG tail to it has to pay Genentech a royalty. Enbrel is made that way, Amevive is made that way, and many other drugs in the clinic are made that way. This is the example I always use

when somebody says, “Why do basic research? What induced all this?” Well, wanting to understand what the homing receptor bound to is what did all this. Who would have ever thought that a patent which will generate—this is not an exaggeration—hundreds of millions of dollars in revenues over its lifetime for Genentech would have come out of this. It is the classic example of why basic research is so incredibly important, because you can’t ever tell what it’s going to come up with.

Hughes: What’s the trajectory here? I see Genentech becoming ever more corporate over time.

Lasky: Oh, it is. It’s becoming more and more corporate.

Hughes: One of the distinctions I see between the pharmaceutical company and the biotech is the spirit of innovation. There’s a certain freedom of research in a biotech company, whereas I think of pharmaceutical companies as a series of boxes.

Lasky: Right. Even after this, for a few years Genentech was very entrepreneurial, but as time went on it definitely got less and less. Now it’s more like the big pharma, and rightfully so. They have a lot of shareholders; they have a lot of responsibility. They have six thousand mouths to feed at the company. It’s a different place. It has to change. I’m glad I was there when it wasn’t like this.

Hughes: Do you remember noticing a change when Kirk Raab became CEO?

Lasky: No. The change was slow and took a decade, I’d say.

Hughes: Is it mainly a function of size?

Lasky: Yes, I think so. It’s inevitable. What you want is to build a big pharma. You can’t have it both ways. You can’t have a fraternity house atmosphere, and you can’t have a big pharma atmosphere. They just don’t go together. I think the trajectory Genentech took was the most successful route from the fraternity house to big pharma, let’s put it that way. The way it happened was the best way it could have happened. There were a lot of bumps on the road. But the end result is a great pharmaceutical company which I guarantee you in a hundred years is going to be Roche, Merck, Genentech. Genentech will always be there. It’s a great pharmaceutical company.

Hughes: Would you go back to work at Genentech today?

Lasky: That’s a good question. I’m not sure. When I first left, I said definitely not. But after being in a different world for a while--you never know until you try it, right? What I appreciate most about Genentech is the unbelievable rigor of the good people. Now, there are a lot of idiots there, don’t get me wrong. Way more bad people than good. But the rigor of the good people was phenomenal. I find it’s very hard to find in my experience outside.

Hughes: Is that so?

Lasky: Very hard. In my new job [as venture capitalist], I have been very disappointed with the level of honesty and rigor that I come in contact with.

Hughes: You're using rigor in a very broad sense? Not just a scientific rigor?

Lasky: Mostly scientific—the level of critical thinking and critical insights and things like that.

[Tape 5, Side A]

Lasky: The new VP of research, [Richard] Scheller, is that kind of person.

Hughes: Yes, he is. And Genentech has a scientist at the helm, too.

Lasky: Right. I think Art needs to stay involved with research. That's key, I think.

Hughes: Does he?

Lasky: He does now, but he didn't during the [Dennis] Henner years. That was a problem. I think overall research now is way stronger than it was five years ago—no comparison. All my buddies, Fred de Sauvage, Vishva Dixit, Andy Chan—these are all really top people. I helped with these hires—we hired a bunch of really top people. So it's definitely very good now.

Hughes: You have a number of patents. How do you weight them in comparison to your papers?

Lasky: The papers are much more important to my ego than the patents. There's nothing quite like discovering something. Very few people get to discover all kinds of stuff like I did. It's all relative. Compared to Goeddel and compared to David Baltimore, I haven't discovered anything. But certainly compared [to others], I've done more than 90 percent of the scientists out there. That's really hard to beat. Now of course, other people find the patents very impressive. In my daily encounters here the fact that I have a bunch of patents, some of which generate gazillions of dollars, is very impressive to people. Most people's patents never do anything. Somebody says, "I take Enbrel." My wife always says, "That's my husband's work." [laughter] That's kind of fun.

When I think about all the papers I published, there are maybe twenty that I would say I'm proud of. But I'm <u>really</u> proud of those; those are great pieces of work. Sometimes you write papers that appear to be great at the time but then subsequently you're proven wrong. These are all really good papers.

Patents don't mean that much but they're great for the company. One always wants to pay their way at Genentech. You either do that by making a drug, which is <u>extremely</u> rare. I mean, how many drugs does Genentech have, and how many scientists have they had? Or this intellectual property thing. I joke with Art about that. I say, "You can't really say that I haven't paid my way because you guys are making a lot of money off my patents." I think that's great. I'm happy for them. Sure, if I were in academics I would get millions of dollars a year or something, but I am really glad. I have to say I'm really glad I was able to pay my way through Genentech with these patents. That makes me feel good.

Hughes: Was the stock incentive program still operating?

Lasky: Options were the big incentive. The employee stock was nothing. But the stock incentive program changed my life. It changed a lot of people's lives.

Hughes: You mean simply in the financial sense.

Lasky: I made a lot of money. Ludicrous. It's not enough. [laughter] Not the way we spend it. It's millions. It's a huge amount of money. How could I have ever done that in my life? If I became an M.D., no way. If I became a professor, it would have been extremely unlikely. It changed my life.

Hughes: If you hadn't had the options as an incentive, what would have happened?

Lasky: The options were hugely important to all of us—hugely. Equal to the scientific publications.

Hughes: So a huge motivator?

Lasky: Huge. Yes.

Hughes: So even though you've said throughout these interviews that the science was primary, or at least that's the way I interpret it, that wasn't quite enough. Science was not the full explanation of what was driving you.

Lasky: Let me clarify. If nobody got options, it would have been enough. In other words, if nobody—Art, Sue Hellmann, Kirk—got options, I would have been perfectly happy getting my salary. The problem was, and this was a big problem, they got a lot of options, and we're doing all the work, is what we [scientists] think. Maybe it's true, maybe not, but that's what we think. Vishva and various other people use the inverted pyramid analogy in that a single discovery by somebody like Napoleone Ferrara [who in 2003 was in the media for his work on the Genentech product Avastin] can generate work for thousands of people and generate billions of dollars in revenue. My little patents, I did that all myself in my own little head, and that's generating tens of millions of dollars in revenues. Without me, it ain't happening. Without Napo, it ain't happening.

Here we get to a darker side of the whole thing. Our perception is that we [scientists] really should get more than we're getting. And yes, it does become a huge motivator, because I want to get millions of bucks for my stuff. Anybody can be a businessman—that's the mentality—but not anybody can discover stuff scientifically. We pushed hard to get big option grants. At first we didn't get them. Martin, in fairness, was a big help for me. Levinson changed my life, though. Levinson just gave me a huge option grant. He's totally changed my life. Art was much better at that. Why? He was a scientist. Art was very good at arguing for his scientists. I remember Art telling me I got this option grant. I couldn't believe it. It wasn't worth anything at the time but I knew someday it might be.

Art would do stuff, like he would take me down to Kirk, and I would show Kirk what I was doing. He would show his scientists off to Kirk when he was VP of research. He wanted Kirk to know that he had a bunch of smart guys here, and they should be rewarded. I have to admit I have a lot of respect and thanks to Art for doing that. Martin

was getting there, but it wasn't really until Art that everything changed. Then, actually, our option grants got pretty big. I was given a lot. Then I got [honored as Genentech Fellow (1999-2002)]. I got a lot of Genentech options from Genentech, and I left a lot when I left, too. Not compared to what I sold, but I did leave a lot. Financial reward was incredibly important. Remember, security is important.

Hughes: Also fairness, too.

Lasky: Yes, fairness was the biggest part of it. What I describe is very accurate. We [scientists] really thought that we made the company. I still firmly believe that, by the way. I think Goeddel and all of us were very similar [in our thinking] along those lines. We really were the heart of the place. Sure, without all the other guys, the drugs would never get developed. Now there's in-licensing, like Rituxan, but without us it's hard to imagine there'd be a Genentech.

Hughes: In your relatively young life, there's been a change in regard to intellectual property, has there not?

Lasky: Right.

Hughes: And a change in attitude toward the financial side of things? Time after time the very earliest Genentech scientists have said to me that in their negotiations with Swanson and Herb there was mention of stock options. It didn't mean anything to them.

Lasky: Right, exactly.

Hughes: Their significance became very clear relatively quickly.

Lasky: Yes. I didn't know anything about them. That was part of the education of being at a place like Genentech versus being in academics. I mean you learn much faster. First of all, Bob was driving a Mercedes. Bob's living in Hillsborough. I'm living in this crappy little apartment. Money was a big issue there. People were talking about money. There are stories very early of people checking stocks, the Quotrek stories. Dave Goeddel got the first thing that you can check your stocks instantaneously. People were <u>very</u> interested in money. That permeated—Art was a big stock trader. He was always interested in the stock market. Money was definitely important. Certainly when I got there, people understood.

I remember the first day on paper that I had a million bucks. Even though I didn't have all the options and all that stuff, it was just incredible. The stock plummeted after that. Money from the start was a big thing. Clearly, people thought they could make money in biotech. We were very naïve about the amounts. The discrepancies between different people in how much they made was a constant problem. People were really pissed off by how much stock people got. We would read the proxy statement every time it came out and get <u>really</u> pissed off about that. The scientists, really until Art, I don't think we were treated very well. I think Art changed all that. Then it got really good.

Hughes: Yet one of Swanson's sayings went something along the lines of, "Genentech's greatest asset walks out every night in tennis shoes."

Lasky: That's right. He couldn't be more correct. But it was also Genentech's most naïve asset. [laughter] I think as time went on we got more savvy, and actually the management had more trouble dealing with that. We were getting uppity, very uppity. They didn't like that. I'll tell you, all the time I was there, I almost came close to looking for another job once. That was it. I was never going to leave. In spite of all the unfairness, it was still the best place to be. So I was never going to leave.

Hughes: But you did leave. What's the story there?

Lasky: Three things: one, twenty years; two, hit fifty [laughter]; and three, it just got too big for me. The twenty years—the implication there is I really did a lot of stuff there, and it wasn't clear what I was going to do next. I know I would have come up with something else, but is it really a big a thrill to do something that you've been doing for twenty years over and over again. Two, the fifty. You're supposed to get a sports car, a mistress, or a new job. So I got the new job. The size—it just felt like it would be harder to get things done my way. One other reason I was able to leave is I felt a lot better when Scheller showed up as vice president of research. I really wasn't too happy with what was going on before we hired Richard. Once I saw Richard, and I knew Richard well, and I respected him, I felt it's okay to go.

Hughes: So you felt a certain responsibility for the quality of the science.

Lasky: Absolutely. I still feel unbelievable loyalty for that place. When Avastin happened and the stock went way up, some people would feel lots of jealousy. I did feel a little bit of that, but I felt really happy for them, really happy. You always check out your own responses to things. I was glad I responded that way. I'm sure some of them there think, you idiot, why'd you leave? But look, I was there twenty years. I did a hell of a lot for the company, so it's not like I have regrets about leaving. Whether this is the right thing or whether I do something else—we're in the valedictory part of the interview—my time there was absolutely the greatest privilege. I can't describe what a great experience it was. To be involved with it and be part of it—unreal. It's like being part of Merck. It's history. I like history, that's why I'm doing this. I think being part of Genentech, you're a part of history. Bob always wanted it to be a billion-dollar sales company. Now, next year, it could be three billion. Poor Swanson never lived to see it. He saw part of it, but what he started happened. It's great.

Hughes: He always wanted Genentech to become a FIPCO, a fully integrated pharmaceutical company. He's got it.

Lasky: He's got it. Sure, Genentech is owned by Roche, but it's not really part of Roche. They're as different from Roche as you can get. Swanson built one of the few fully integrated pharmaceutical companies from scratch. That's amazing.

Hughes: And he saw that.

Lasky: He did see that. He saw the billion-dollar sales. But he wasn't happy about how everything turned out. No one will remember Kirk Raab. Everyone will remember Bob Swanson. His place in the pantheon of history is set. The guy started an industry. How many people can say that? In spite of the tragic thing that happened to him, he's done something most people can't say they've done.

Hughes: A good place to stop?

Lasky: Yes.

[End of session]

Front, left to right: Diane Pennica, David Botstein, Avi Ashkenazi
Back, left to right: Stuart Builder, Richard Scheller, Arthur Levinson, David Goeddel, ?, Laurence Lasky

SALLY SMITH HUGHES

Sally Smith Hughes is a historian of science at ROHO whose research focuses on the recent history of bioscience. She began work in oral history at the Bancroft Library in 1978 and joined ROHO in 1980. She has conducted interviews for over 100 oral histories, whose subjects range from the AIDS epidemic to medical physics. Her focus for the past decade has been on the biotechnology industry in northern California. She is the author of *The Virus: A History of the Concept* and an article in *Isis*, the journal of the History of Science Society, on the commercialization of molecular biology.