Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Program in the History of the Biological Sciences and Biotechnology

Diane Pennica, Ph.D.

# t-PA AND OTHER RESEARCH CONTRIBUTIONS 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.

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

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Diane Pennica

*Photo courtesy of Diane Pennica*

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# 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

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

August 2004

## ORAL HISTORIES ON BIOTECHNOLOGY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.
Lawrence Lasky
Arthur Levinson
Steven Rosenberg
William J. Rutter, volume II
Axel Ullrich
Mickey Urdea
Pablo Valenzuela
Keith R. Yamamoto

INTERVIEW HISTORY—Diane Pennica

Diane Pennica believes that her greatest contribution to Genentech is the cloning of t-PA, an acronym for the "clot-buster" tissue plasminogen activator, sold under the marketing name Activase. The story she tells in this oral history is one of science, the science of isolating and cloning protein-producing genes, which then might be made into marketable products. She has consistently in her long Genentech career—she arrived in 1980—made it her policy to stick to science because it is what she does best and because there are others whose job it is to patent, develop, and sell. The reader will have to turn to other oral histories in this series—those with Kirk Raab and Jim Gower, for example—to learn of the subsequent development and marketing of t-PA, a product that Genentech expected to be a blockbuster.

This oral history tells of Pennica's single-minded pursuit of t-PA after a chance meeting in which she learned of the molecule's potential for salvaging heart-attack victims through the lysing of blood clots. But the naturally occurring substance occurred in amounts too small to be useful; the gene had to be isolated and cloned. Genentech in 1980 was a cloning center par excellence. And Pennica was to demonstrate that Dave Goeddel was not the only Genentech scientist with "golden hands." We learn here of Pennica's ability and astounding tenacity—fifteen hours a day, seven days a week, for two years—in the grueling and ultimately successful effort to clone the gene and isolate the complicated t-PA molecule. In 1989, she and three others received the Inventor of the Year Award from the Intellectual Property Owners Foundation.

Although Pennica and others give pride of place to her work on t-PA, this oral history makes clear that she has other scientific accomplishments to her credit, including work on urokinase, tumor necrosis factor, p53, uromodulin, and cardiotropin. These are not familiar substances; Pennica introduces them in words meaningful to the non-scientist.

She also speaks cautiously of what it was like to be one of the few women at Genentech in what, at the start, was an aggressively male environment. She was and to some extent remains a being apart, not only because of corporate culture but also because of her isolating focus on the doing of science and, more recently, on the mentoring of the young people in her laboratory.

Oral History Process

Three interviews were conducted in 2003 in Pennica's office adjacent to her laboratory at Genentech. Although she claimed nervousness, what in actuality was apparent was Pennica's intent to tell her story chronologically and well. That she did, referring at times to her meticulously kept notebooks and laboratory records. She reviewed the interview transcripts, editing for clarity but not changing content. By agreement with Genentech regarding only the oral histories it supports, its legal department receives transcripts of all interviews to review solely for current legal issues. As in all other instances to date, no changes were requested in the Pennica transcripts.

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

Faulhaber, James D. Hart Director of The Bancroft Library, University of California, Berkeley. The catalogues of the Regional Oral History Office and many online oral histories can be accessed at http://bancroft.berkeley.edu/ROHO/. Online information about the Program in the History of the Biological Sciences and Biotechnology can be accessed at http://bancroft.berkeley.edu/Biotech/.

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August 2004

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The Bancroft Library

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Berkeley, California 94720

## BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

Your full name DIANE PENNICA

Date of birth 7-25-51 Birthplace FREDONIA, New York

Father's full name FRANK James Pennica

Occupation CARPENTER Birthplace FREDONIA, New York

Mother's full name MAMIE MARIE Pennica (deceased)

Occupation Administrative Assistant Birthplace FREDONIA, New York

Your spouse/partner not married

Occupation — Birthplace —

Your children NONE

Where did you grow up? FREDONIA, New York

Present community BURLINGAME, California

Education Ph.D University of Rhode Island 1977

B.S. State University of New York College at Fredonia 1973

Occupation(s) Senior Scientist Molecular Oncology Department

Genentech, Inc.

Areas of expertise CANCER Research / molecular biology

Other interests or activities enology

Organizations in which you are active American Association for Cancer Research

SIGNATURE Diane Pennica DATE 5-31-04

**INTERVIEW 1: JULY 8, 2003**
[Tape 1, Side A]

Hughes: Dr. Pennica, let's start way back with your grandparents on both sides. Tell me a little bit about where they came from and what they did for a living.

Pennica: My grandparents on my mother's side were born in Sicily in a very small town called Vallelunga, and they came over when they were both eight years old and met and got married. My grandfather worked in the steel mill in Fredonia, New York, which is where I grew up. My dad is a carpenter, and he built the house that I grew up in.

Hughes: Is that so?

Pennica: So we moved into that house. He built about a hundred houses in our hometown, Fredonia, New York. My grandfather worked in the steel mill, and my grandmother had five children. On the other side, my dad's father was a blacksmith, and my grandmother on my dad's side had ten children—eight daughters and two sons, my dad and my uncle. It was a huge family.

Hughes: But not unusual for the time, right?

Pennica: No, not at all. My dad will be eighty in September, 2004, so, yes, they had to work to raise money to feed the family. I grew up in an Italian household where everybody got together on Sundays and had spaghetti and meatballs [laughs], and we had a huge garden when I was growing up where we grew everything from corn to peas to carrots and many other things in the garden. We always had fresh vegetables, so it's disappointing when I go to supermarkets here.

Hughes: Yes, I can imagine.

Pennica: Because nothing tastes the same as a fresh-picked strawberry or a cherry off the tree. It was a fun time growing up there.

Hughes: Was it an Italian community?

Pennica: Pretty much, in Fredonia. There's a lot of Italians there, and all my relatives stayed in the same area. So we always got together with all my aunts and uncles, and we have a huge extended family there, so it was nice.

Hughes: And are they still largely there?

Pennica: Most of them are still there, those who haven't died. They are still in the area; they didn't travel very far. We moved into the house my dad built there when I was one year old.

Hughes: Was carpentry considered a step up from the steel mills?

Pennica: Probably, I don't know how he and his brother decided to build homes, but they built a lot of homes in our hometown, and my dad would show us all the homes that he'd built. His brother's wife died when she was very young of lung cancer. The two of them

would build a house, my dad's brother would move into it, they would start another one, and he would move into that until they sold the house. If I had a second career, that's what I would do. It's such a satisfying type of career.

Hughes: Do you go back?

Pennica: Yes, I was just there a couple weeks ago. I went there for a week. I usually go back a couple of times a year, depending on my trips back East; so this was a nice vacation, gorgeous weather—I don't miss the hot, humid summers or the freezing cold winters, because we get lake-effect storms, six feet of snow in the wintertime, but California weather's perfect for me. [laughs] Hard to beat; the prices are horrible here, but it's nice to go back and visit my hometown.

Hughes: I bet. What was the attitude about education?

Pennica: Well, my dad said, "I have four daughters, and if you want to go to college, which I hope you all do, you have to work to pay for it." So I worked. I started working when I was eleven years old picking berries in the fields, picking strawberries and blackberries and currants, and I made sixty dollars for the entire summer, one summer, working from six in the morning to six at night. I was the fastest picker and made the most money. The entire summer, my paycheck was sixty dollars. [laughter]

I bought my first transistor radio, and boy, that was the hardest work I've ever done in my life. It was backbreaking, but there were people there doing that for a living, to support their families, because they brought their kids there, and I thought, "How sad." You know, I was doing that more for fun, and I was so thrilled that I could make that kind of money. To me that was a huge amount of money, for a whole summer! [laughs] Sixty dollars! So that was my first job. I then worked to support myself through college as a bookkeeper at a Sherwin-Williams paint store, and I also worked with my mom a bit. She worked for the Board of Cooperative Educational Services as the head administrative assistant. It was a school for people who didn't want to go to college; they did trade stuff, beauty culture and masonry and plumbing and things like that. I helped her do administrative work while I was going to college. I went to college at Fredonia State—State University of New York there.

Hughes: And lived at home?

Pennica: And lived at home, right, because my parents couldn't afford to send me away to school. I was their first daughter and I wanted to go to college, so I put myself through school. It wasn't that expensive if you lived in the town.

Hughes: Right. Did you know what you were interested in?

Pennica: No, not at all. My dad said, "I think you should be a teacher because it's a great career for a woman." I remember his words, he said, "You get the summers off. It's a great thing." So I started out in college at Fredonia State as an elementary education major for two years but took science courses on the side. Every time somebody asked me what I was going to major in I would say, "Elementary education," and I would have an uncomfortable feeling, something just wasn't right. I don't know why, and I wasn't doing that well in the education courses—you had to memorize the school system

politics in the 1800s, and I just didn't find that exciting. I think teachers are a wonderful group of people, because without them I wouldn't be where I am today, but it wasn't for me.

So I was taking science courses, and then I took a course from a man named Dr. Kevin Fox, who taught a microbiology course at Fredonia State. He was so enthusiastic, and so much fun. He had a spark in his eye, and he said, "Why don't you work in my lab after class when you have breaks, and just see if you like this stuff?" So I was thrilled; I did growth curves of bacteria, I did little things in the lab. Then he got me into somebody else's lab, Dr. Irv Schmoyer, who was doing a wonderful thing. He was trying to look for the cause of cystic fibrosis. He wanted to develop a diagnostic test for parents who were carriers of the cystic fibrosis defect. He had a son who died when he was three years old. I started working in his lab, and he had this great idea that actually worked. He had an oyster tank in his lab, where he used the oyster gill cilia for a diagnostic assay. The cilia are little fine hairs that move the food in for feeding, and normally these cilia beat very synchronously like wind blowing over a wheat field. You can imagine, they're all moving in one direction. If you take serum from a normal person, it didn't do anything—the cilia beat very regularly. However, if you took serum from either him or his wife, because they knew they were carriers, the cilia would get all entangled, and beat asynchronously.

Hughes: How interesting.

Pennica: So we published a paper. I was just thanked, I wasn't one of the authors on it, because I was only doing little things to help. He fractionated the serum, and he found one of the fractions caused this asynchronous beating of the cilia in heterozygous cystic fibrosis carriers. So that was very exciting. Between these two men, Kevin Fox and Irv Schmoyer, they said, "Why don't you consider changing your major to science?" Because I was always excited about going into the lab and helping out, in my junior year, I decided to switch my major. So I crammed all the science courses in my last two years of college—I was getting A's in the science courses, and C's in the elementary education classes because I was bored.

Hughes: [laughs] How did you happen to take the science courses on the side anyway?

Pennica: Well, I think it was probably required; I took statistics, I took economics, and one of my teachers—his name was Dr. Haitani—he said, "Why don't you become an economics major?" I was getting A's in his course, too; that was fun. But he said, and I'll never forget his words either, he said, "You should switch your major to economics." He said, "It's a career full of men." [laughs] I thought to myself, "Why should that be important?" But he was a nice man, and he made it interesting and exciting, but I didn't have the same sort of feeling that I did about science. I hadn't seen Kevin Fox in, oh probably fifteen years, and just two weeks ago when I went back to Fredonia, my sister and I went for a walk—we always walk around Fredonia just to see the town—we were walking along, and I see this man in a baseball hat, and I say, "Good morning," just because it's a friendly town. I got an instant recollection, and I looked back and I said, "Kevin Fox?" And he was my old teacher that I haven't seen in probably close to twenty years. It had been such a long time, yet he still looked the same.

Hughes: Did he remember you?

Pennica: Yes. Well, I had a baseball cap on and sunglasses, so I said, "Diane Pennica," so he gave me a big hug, and we talked for about twenty minutes. I said, "Because of you, I became a science major." I told him that he made science so much fun and so exciting. So I think teachers are wonderful—it just wasn't a career for me.

Hughes: Were these men a little unusual? I imagine that Fredonia is rather a small town.

Pennica: Very small town.

Hughes: And the university is a small regional university?

Pennica: Yes, it's one of the SUNY schools.

Hughes: So it wasn't unusual—because that research on the cilia sounds like rather a significant discovery—it wasn't unusual to have science being done of that kind of quality in a state university?

Pennica: Well, it's hard to know because at the time, I didn't know what science people worked on. To me, it was a perfect project for him because he had an emotional commitment—

Hughes: Connection—

Pennica: Connection to something like that, and Kevin Fox was doing some interesting research on mice, and I learned how to handle mice from him. He was working on librium and valium, which, he said, are supposed to calm people down, and instead he found they were making the mice more aggressive. So I thought that was an interesting project—all these people were doing interesting work. I took another class from a botanist and that was interesting to me too. So I don't know if it was cutting-edge science or not, but it was certainly fascinating to me, so I totally switched my major thanks to these men, who convinced me that science was exciting. If I had boring teachers, I probably would have stayed in elementary education.

Hughes: Amazing thought, isn't it?

Pennica: Yeah.

Hughes: What did your parents think of your switch to science?

Pennica: Oh, they thought it was great. They could tell I was more excited about it. They would ask, "What are you going to do next?" I didn't know. I didn't know what I was going to do next.

Hughes: Had you ever thought of graduate school when you started out?

Pennica: Never, never, never. Kevin Fox and Irv Schmoyer convinced me—I thought, "Oh, I'll just get a master's degree," and they said, "Why not go for your Ph.D.?" So I interviewed at schools, and this is again another tribute to people who can either recognize somebody who might be excited. I got accepted at Ohio State, and Dartmouth, and the University of Rhode Island, and everybody said, "Oh, Ohio State's a big-time school, it's great, it's wonderful." But somebody told me that I should go

interview at these places just to see what they're like. At the time a plane ride was so expensive, I had no money, and I was using all my money to pay for books and college at the time, but I thought it was a good idea. So I flew to Ohio State, and I was shuffled around from person to person, nobody really paid attention to me—I don't even remember what they said, but I felt disconnected. It was such a huge place, that I came back and I said, "Well, it was interesting."

Then I went to the University of Rhode Island—I decided I didn't want to go to Dartmouth, I don't know why—I flew to the University of Rhode Island, and the guy who had an opening in his lab for graduate school, Paul Cohen, was on sabbatical in Boston. He took time off to meet me. He was so excited about his research. He was, again, another person with a spark, and he said, "Let me tell you about this project, and let me tell you about this project," and I was hooked. I did not get that feeling at Ohio State. He was just so incredible that I decided to get my Ph.D. from him, because he was ready to jump out of his chair at every little experiment I did. "Oh this is so exciting!" [laughs] He was already plotting the data in his head before I could even get back to my desk. As data was coming off the scintillation counters, he was so excited.

Hughes: What was he? Was this molecular biology?

Pennica: It was microbiology.

Hughes: Microbiology—

Pennica: Yeah, and we were studying viruses at the time, and actually bacteriophage, viruses that infect bacteria. We were looking at—you wanted to know what I was studying?

Hughes: Yes, yes, I do.

Pennica: Oh, it's so long ago, but I do remember. We were studying messenger RNA stability and decay in T-4-infected *E.coli*. So when the virus infects the bacteria, it takes over the machinery of the cell, and it makes its own RNA. We were looking at how that RNA behaved, how long it lasted in the cell, and how quickly it got degraded. And that was fun for me. He was just the most enthusiastic teacher. He's still doing great work now—but he was terrific, and he convinced me, "Oh, just don't stop at getting your master's, just go on and get your Ph.D." So I did, because of this teacher encouraging me. I didn't know what I wanted to do, but everything just fell into place. I always loved working in the lab. I felt I was good at it, and it was really fun.

Hughes: Was there a science community at the university, or was Cohen kind of a fish out of water?

Pennica: Well, there was a little community there that was in the biology department. I took courses from the biophysics guy. There was another woman there who was just thinking about recombinant DNA, because plasmids had just been discovered. One question that she asked during my thesis oral exam that I'll never forget and that I didn't know the answer to was, "What do you think plasmids could be useful for?" Of course, that's [laughs] all biotechnology; I said, "I don't know, but—"

Hughes: What year was that?

Pennica: I got my Ph.D. in four years, so—

Hughes: Nineteen seventy-seven.

Pennica: Seventy-seven, right; so that's before [Herbert W.] Boyer and [Stanley N.] Cohen, and [pause] Swanson—

Hughes: No, it's not before—Genentech is formed in April of 1976.

Pennica: Seventy-six, right.

Hughes: So Genentech is barely off the ground. Cohen and Boyer's first paper was 1973—

Pennica: Oh, okay.

Hughes: But this shows you, I mean it gives you an idea of how this, what we now recognize as revolutionary, science takes a while to diffuse.

Pennica: Oh, exactly.

Hughes: You're not the first person to say that. I mean, it's not as though all of a sudden 1973 or even 1974 everybody switches to recombinant DNA.

Pennica: Exactly. So we were studying RNA stability. I had never heard of a plasmid at this point. I didn't know about restriction enzymes, we weren't using them. We were very focused on what we were doing, so I didn't know about what was going on with recombinant DNA. But this woman said, "Plasmids, could they be useful for anything?" She must have read all of this stuff, and I had no clue about them because I just read the papers that were focused on what I was doing, not—

Hughes: Was the work that you were doing with bacteriophage and the messenger RNA, was it a microbial/biochemical approach, would you say?

Pennica: Yes, right. And because of that, it helped me get a job here, because that's what they were interested in. They wanted somebody who knew how to work with RNA because that was critical. That was one of the things that helped get me hired, I believe.

Hughes: Yes. But there's a step in between—

Pennica: Oh, did I miss something?

Hughes: Well, you were at [Hoffmann-La] Roche.

Pennica: Oh, right, yes, yes.

Hughes: Tell me how that happened.

Pennica: Yeah, the story of how I got to here is also an amazing story.

Hughes: Well, we'll tell that next.

Pennica: But Roche. Paul Cohen had a friend at the Roche Institute of Molecular Biology, Herb Ennis, and he was also doing similar work, but with animal viruses—studying stability and messenger RNA decay in vesicular stomatitis virus. That's a virus that's similar to hoof and mouth disease. [pause] So we were doing similar things, so it was a natural progression for me to go there, learn about a slightly different system, but do similar experiments. That was a good fit, so I went to the Roche Institute and did my postdoc work there for two years, and that was a lot of fun. Herb Ennis was a very meek and mild man, and we had a lot of fun together. There was a meeting—which tells you how I got here—there was a meeting in London on rhabdoviruses. This family includes rabies virus and vesicular stomatitis virus, which I was working on. A friend of mine upstairs at the institute said he was going to go to this meeting, and he said, "Why don't you try to go?" I asked my boss, and he said, "I don't have the money to send you." I had seen an advertisement in one of the science magazines, where they said, "If you have some exciting research, we have some fellowships available for $500." And I said, "Herb, look at this, maybe I can get some money to go to this meeting." He said, "Oh, people never get those, don't waste your time." I didn't listen to him!

So I wrote a little paragraph on what I was doing. I was working on VSV stability and decay, and we had found something very interesting. This virus, VSV, has only five messenger RNAs, that it uses to take over the cell, and nobody up to that time had ever separated two of them. They were of similar size and charge and molecular weight that when you ran them out on a gel, they co-migrated together. So we devised a urea agarose RNA gel system that I would run in the cold room for about eight hours. We would pour these huge long gels, and finally, we were able to see a very, very thin separation between these two RNAs on the gel. I was able to cut them out of the gel, put them in a test tube, and figure out which RNA made which protein. This was so exciting, because nobody had ever done this. So that was one of the first papers I published at Roche, saying, identification of this band makes this protein in this virus. Nobody had ever done that before. I wrote this in an abstract, because I was very excited, and they wrote back and said, "We'll give you the money for the conference." Herb was floored! He said, "I can't believe it." So I said, "Well, if you don't try, you don't get!" He was a shy, meek person, but I said, "I want to try. Why not?" So, my friend Doug Testa, who was also working on some other virus, and I went to London together.

I didn't apply to give a talk at the meeting, but they just wanted to know what you were working on, and why you should be given the money, and why this conference was relevant to you. Doug said, "Diane, when you go to a meeting"—this was my very first meeting—"always bring a few slides." I said, "Why? I'm not going to talk." I was shy, very, very shy—still am. [laughs] But he said, "Bring a few slides." He said, "Well, if you're talking to somebody and they ask about your research, you can show them your data. I mean, you've done this incredible thing; you've separated these RNAs. Nobody knows about this stuff yet"—I don't think our paper had come out yet—"so this is really exciting. I said, "Okay, fine, good idea." So we went to the meeting, and he said, "I'm going to ask"—I was telling him about this stuff on the plane, and he said, "This is incredibly exciting, so I'm going to ask one of the organizers if you can speak." I said, "No, no, no, please; I haven't prepared a talk—besides, I'm a nervous wreck, I didn't want to do it." He said, "Just let me ask." He went to the back, and he said, "You've got to let Diane speak. She's got something really relevant and pertinent to this meeting." The guy said, "I'll give her five minutes, five slides." Now this is very unheard of, to

put a totally unknown speaker, somebody they don't even know on the program. You normally submit abstracts, and tell them what you're going to say—they didn't know what I was going to say up there. But Doug Testa convinced me—again, somebody was pushing me—to do this. And I said, "Oh God!" So I went back, he said, "They're putting you at the end of the session and letting you speak for five minutes." And I go, "God!" I went and put seven slides back in the projector, although he told me only five! And I probably gave the best talk that I've ever given in my life because I was so nervous, so hyped-up. And in five minutes I was able to tell the story—here's the virus, there's five RNAs, I was able to separate them, this is what they look like separated, I put them in a test tube, I translated them, this makes this, this makes that, boom. And everybody was floored, and they clapped, and I got so many people coming up saying, "That was an incredible talk," because most people talked for half an hour, and you often get bored.

Hughes: Yes, yes.

Pennica: Five minutes is probably a good thing; you just tell the essence, and not a lot of background. My five-minute talk was the key to my getting a job at Genentech, because in the audience there was a guy from the Centers for Disease Control in Atlanta, Jack Obijeski, whom you may have heard of.

Hughes: I've heard his name, yes.

Pennica: Jack came up to me after my talk and said, "So, you think you can separate RNAs? It looks like you're good at working with RNA." I said, "Well, I did it once, sure I can do it." And he said, "We're working with a rabies virus—can you do the same thing with that?" And another virus, I can't remember the name of it, it just slipped my mind. Related, again, related. But they couldn't separate the RNAs. And I said, "Sure." He was at the CDC in Atlanta, and he sent me the RNAs, and I did the same thing, separated them, translated them, and determined which RNA made which protein. We published a paper. Then he said, "There's a new company that's just started out that has been contacting me, called Genentech, and they are interested in hiring people, can I give them your name? Because they want people who know how to work with viruses. They're actually trying to make a vaccine for rabies, and you've been working on it, and you know how to work with RNA, that's what they're interested in." And I said, "Sure, give them my name."

Hughes: Never, of course, having heard of Genentech—

Pennica: Never having heard of it. I had no clue what they were even about. And they gave me a call. So because I persisted, wrote this abstract, gave that five-minute talk, Jack and I collaborated on the rabies project, which he told Genentech about, and they gave me a call. Mike Ross called me and said, "We want somebody who knows how to work with RNA, who's worked with viruses." They had me out there for an interview, and I got hired. So, just a series of little things, and people pushing or helping along the way got me here. I gave a seminar in Building One, this tiny little room, and people were lying on the floor because there weren't enough seats. I told the story of separating the viruses, and all the RNA work that I had done. I also interviewed at Chiron, and they did not hire me.

Hughes: Isn't that interesting?

Pennica: So, I don't think they were doing RNA work, or that wasn't something that they were interested in, I don't know why. But, Genentech offered me a job.

Hughes: Interesting. Well, before we leave Roche, say something about the Roche Institute: What was the atmosphere? Was it closer to what you had experienced in academia, or were you beginning to move more into a corporate sort of culture?

Pennica: No, it was academia, totally.

Hughes: It was, totally.

Pennica: Yes, because the institute was completely separate from the company. The company seemed different; we were a little building on the hill that was very isolated, and I felt it was a little research center, that we were doing what we wanted.

Hughes: Oh, is that so?

Pennica: I think so—they just had a research institute that I thought was great because the people were doing lots of exciting research. But, I don't know if any of it translated down to what was happening at the company itself.

Hughes: Well, the fact that you weren't aware says something right there.

Pennica: Exactly. It seemed very separate. And we didn't mingle with them; we had our own little tower. It was separate. It seemed very academic to me. And again, I just focused in the lab, and that's all I did.

Hughes: Did you have any thoughts, when you got the job offer from Genentech, about, oh, wow, this means I'm leaving academia, and I'm moving into the corporate world?

Pennica: No, I was so naïve. Again, that's probably a good thing because people are struggling now, oh, shall I stay in academics, should I stay in industry? I never even had that thought for a second because I didn't know what Genentech was. I didn't know. [pause] Again, I think it was probably better for me not to know what it was all about. To go all the way across the country, and—[pause] You know, I was interviewed by Herb Heyneker, Peter Seeburg, I believe, I don't know if Dave Goeddel, my eventual boss, if he interviewed me. At the time I think he was in the middle of an experiment—

[Tape 1, Side B]

Hughes: What about the new genetic technologies at Roche? I mean, were people using recombinant DNA, or—

Pennica: I think they were starting to but, again, I had blinders on—I was so focused on what I was doing, that I wasn't the type to go down the hall and say, "Hey, what are you doing?" I probably should have because I would have been more exposed to that. I think people were using restriction enzymes there. And eventually somebody who went to Chiron, Mike Innis, I think he was starting to do that sort of work. But again I always

worked so intensely that I didn't have time to run around and ask people what they were doing. I would hear their seminars. We had a Nobel Prize winner at the institute, Severo Ochoa—

Hughes: Oh, yes, I know.

Pennica: He was two doors down from my lab, and I would go in and talk to him occasionally.

Hughes: He was approachable, then?

Pennica: Oh yeah, he was a really nice man; he seemed very old [laughs] at the time. He moved very slowly, but he was great. Everybody was nice there, and I had a really good time. It was almost too short—most people do postdocs for four years; I was there about a year and a half. And that was it, but I did publish papers. I don't remember how many—it's on my CV. But it was a fun place to work, and Herb Ennis was a great guy to work for, too.

Hughes: It sounds as though, if you were not even going down the hall very much, that you were working very intensely.

Pennica: Yes, yes.

Hughes: Is that your style?

Pennica: Yes, and my boss said, "You have no clue what's going on in the rest of the company," because I usually don't! [laughs] So, that's a good thing and a bad thing. But I tend to focus and not get involved in politics, and I think it's good for me.

Hughes: Can you remember your first impressions of Genentech?

Pennica: Yes. [pause] My first impressions—when I was hired? Or before, as I was being interviewed?

Hughes: Well, maybe when you were being interviewed, how did it compare with the other institutions that you'd been in? Did this group seem different in any way?

Pennica: Yes, more laid back. Chiron was very formal. There was a beautiful conference room, lots of people in it, very formal thing. And the room I gave my seminar in at Genentech, people were lying on the floor because it was such a tiny room. It seemed very informal, and I became less nervous as I kept talking because they seemed so laid back. But they asked a lot of questions, and they seemed interested. It just seemed like they were a bunch of young people, but I didn't know what the company was about, until I talked to them later, and they told me, "Here's what were trying to do."

Hughes: Was [Robert A.] Swanson at that first meeting?

Pennica: I don't think he was at my seminar. I don't even remember—Mike Ross was there, Herb Heyneker, Peter Seeburg was laying on the floor, I think Axel Ullrich was there, Hugh Nile. I think Hugh Nile was interviewing at the same time, on the same day he gave a seminar as well; I think he heard my seminar. There was a handful of people there, so

just the people who were involved in hiring me—like Herb Heyneker, who was my first boss here—were in that little room.

Hughes: Does that mean that, at least at that stage, that the scientists pretty much hired the scientists?

Pennica: I think so. Yes.

Hughes: And they could do that independently of Swanson?

Pennica: Well, I don't know if that was the call—the letter that I got saying, "We'd like to hire you," was from Bob Swanson. I probably still have that letter. I'm sure I do; I've never thrown it away. Herb Heyneker was supposed to be my boss, but I think it was up to the scientists to decide whether the caliber of the science of the people who they were trying to hire was good enough.

Hughes: Yes, so probably somebody or somebodies then went to Swanson and said, "This woman is good. She fits right in, and we should hire her."

Pennica: Probably, yeah. I would hope that's what they said!

Hughes: Why Heyneker?

Pennica: Who knows what the formality was at that point. He either had a position in his lab, or the project he was working on needed someone who knew how to work with RNA. I don't know why it wasn't Dave Goeddel—I eventually did work for Dave—but I don't know how it was decided. Because there weren't that many people there at the time. I could have worked for Peter Seeburg or Axel Ullrich or Dennis Kleid. Dennis may have been at my talk, I don't know; he would probably remember if he heard my first seminar. I don't remember if he was in the room because I didn't know these names and faces, but I bet Dennis would remember. You might have met him, Dennis Kleid—you've interviewed him, too.

Hughes: I've interviewed him, yes, yes.

Pennica: So, he would remember that.

Hughes: And then, what were you assigned to do in your windowless lab? [laughs]

Pennica: Interesting. I was assigned to work on the very first contract project that Genentech had with a German company called Grünenthal, and it was to clone urokinase—I didn't know what that was at the time—a serine protease that is made in the urine that dissolves fibrin. They were thinking of using that for potential treatment of blood clots. On that project, we were collaborating with this company and getting protein sequence, and we were using cells—I can't remember the name of the cells—human embryonic kidney cells, I believe, to extract the RNA to see if we could clone urokinase. Bob Swanson, because it was our first project, was very adamant about doing this well, you know, doing a good job, because he wanted to make a good impression since they were giving us money.

Hughes: Why do you call it the first project?

Pennica: It probably wasn't the first—it was my first project.

Hughes: Oh, your first project, I see.

Pennica: My first project. It might have been the first contract, I don't know. You probably know better than I do whether we had contracts with growth hormone, or somatostatin, or insulin—I don't know if we had contracts or we were just doing them.

Hughes: Certainly the insulin contract came after the cloning.

Pennica: Right.

Hughes: Genentech had to prove its stuff, that it indeed could do that.

Pennica: Grünenthal was just the opposite, I think. They wanted to clone this, and they were giving us money before we cloned it.

Hughes: Well, and it probably does relate to that past history, 1980. See, growth hormone had been cloned too, so probably Grünenthal knew about this small company that seemed to be the place to go for cloning.

Pennica: Yes, yes. I'm sure that that's probably true, but I thought Bob had said this was our first contract.

Hughes: That could be, that could be.

Pennica: His office was as close as the one here to my lab, so he would be in my lab all the time asking, "How are you doing?" and "What's going on?" and "What's new?"

Hughes: How much freedom were you given? Was this really your—other than Swanson looking over your shoulder, I mean.

Pennica: They left the experiments up to me, for sure, and I was working with another research assistant there, Bill Holmes, who eventually got his Ph.D.—not at Genentech, he got it in Belgium and that's a different story—but the two of us were working on urokinase together. He was working on one aspect of the cloning. I was doing the RNA work and doing similar things to what I was doing at Roche, since I had that expertise. I would extract RNA, see if it would make in a test tube urokinase that we could detect with an antibody. So they didn't tell you what experiments to do, I was just doing them.

Hughes: And was that all right with you? Or was that a little intimidating?

Pennica: Well, I wasn't sure where to start at this point, but I knew the steps I had to do, at least at that point. Then, I'd been at Genentech one month, and they said that they needed somebody to go to this fibrinolysis meeting in Sweden because they had heard rumors about somebody working on a blood-clot dissolving substance. I don't know if they knew the name of it; at that point they might have. But Gordon Vehar said, "We need somebody to go." Dave couldn't go, he was too busy, Herb had a family, everybody else

was too busy, and I said, "Sure, I'll go to this meeting." They said, "Find out what is known, what's going on—there might be something that's better than urokinase, or as good as, that we should know about it." And that's where the story picks up that you had heard, that they sent me to this meeting, and by accident I got into this private meeting by mistake. I don't know if you wanted me to—

Hughes: Tell the story because others don't know it.

Pennica: Right. So it was my first, no actually second now, because I'd been to London already, that was the second—the first meeting was how I got to Genentech, by giving that little five-minute talk. So this was my second international trip, and I was very nervous. I am so particular about time. I worry about being late, it was instilled in me when I was growing up, be on time, be on time, be on time. I always keep that in the back of my mind. I'm always early for things, and I think that's better; to this day I try to be early for things because I tend to meet people who I never would meet otherwise. And so, I get off the plane and, since the meeting started the next day, I wanted to map it out; I wanted to walk to the meeting ahead of time, just so I wasn't nervous, and try to figure out where it was because I knew it was a little out of the way. I thought, if I did this I'll be confident in the morning, because I'll know exactly how long it takes to get there, since I mapped it out ahead of time. I start checking into the hotel, and I asked the desk clerk, "Can you tell me where this meeting is, this fibrinolysis meeting?" She didn't know what fibrinolysis was; she just gave me a quizzical look, and said, "Oh, the meeting of the doctors!" I said, "Well, yes, that's close enough!" [laughs] She said, "That started today," and my heart sank, because I thought, oh my God, I got the wrong day, it's the time change, I'm totally messed up. I ran up to my room—I had a hot-pink sweatshirt on, just similar to this, and black pants, and threw my suitcases down, didn't do a thing, and ran over to where she said to go. I peek in the room, and there's a big, conference-room table with about thirty guys—I didn't see any women in there—all sitting around this big table. And I sat in the back, I just walked in the back and they started looking back, and I took out a notebook and started taking notes. And they kept looking back at me but continued with their talks. About ten minutes after I got there, Desiré Collen gave a talk and said that he had melanoma cells that make this substance he called tissue plasminogen activator. He said he had an antibody against it, and he had purified protein. And he had treated a woman who had deep-vein thrombosis, a blood clot in her leg, and the blood clot dissolved with this substance. And here was exactly what Genentech had sent me to hear.

Hughes: Right.

Pennica: And Genentech said, "See if anyone has a cell line. We need the cell line to extract the RNA; we need purified protein, we can try to determine the structure of it by conventional protein sequencing methods, and an antibody is also very helpful, because then you can detect the protein in various ways."

Hughes: So Vehar had told you all this?

Pennica: To try to see what they have, what reagents; these are the things that we needed to clone anything: You need a cell line, you need antibody, you need pure protein. So I was tuned to those things, and here this guy got up there and said we have all these things, and I'm taking notes. Then there was a break, and somebody came and said, "Can I help you?"

And I say, "Oh, I'm really sorry, my name's Diane Pennica, I'm from Genentech, and I am late for this meeting. I don't know how I messed it up." He said, "Oh, no, this is not the real meeting, this is a pre-conference session." It turns out—I didn't know this—at the beginning of the meeting they have all the hotshots, the head groups of the labs, or the famous people to talk about their work. [laughter] The real meeting was three hundred people; there was only about thirty of them in this little conference room. They said, "But you're welcome to stay." I said, "Great!" He said, "And, you can join us for dinner if you'd like later!" [laughs] They had dinner at a castle, and I got to meet Desiré, face to face. They were all M.D.s, I'm sitting at this table—I've been at Genentech one month—I'm describing to them what cloning is on napkins, all excited, and saying, "This is what we can do, and this is what we've done." I had never cloned anything in my life, but I didn't tell them that.

Hughes: [laughs]

Pennica: And I said to Desiré, "Would you consider having us try to clone t-PA?" And he said, "Oh, it's a huge molecule, the only thing you guys have done is growth hormone, that's really tiny, we know how big t-PA is." And I said, "We can do it!" I had no idea if we could do it, but I figured, you know, be enthusiastic, and that can't hurt. So we talked at dinner, and I met the guy who first crystallized urokinase, a really famous man, I don't even remember what his name is now. But I met all these guys who were instrumental in the fibrinolysis field. The real meeting was three hundred people, and I might not have ever met Desiré, I might have been too shy to go up and speak with him, I might have only heard his talk, gone back and reported, "There is a guy who has the reagents we need to clone t-PA." But I—

Hughes: Yes, but you short-circuited—

Pennica: I short-circuited everything. I got face-to-face with this guy, and we talked, and we got along. The real meeting was almost a blur because I was so excited that I had met this guy. I don't remember the other talks. I remember him getting up again in the real meeting and talking again. I drilled in my head what he was saying.

Hughes: What was the attraction as far as Collen was concerned? Why was he listening to this young thing? Who wasn't part of the in-group either?

Pennica: Right, I was not part of the in-group. Who knows? I really don't know. But I think that he was intrigued enough with the technology, that he was also a very enthusiastic researcher. He had a spark, and he wanted to make a big splash, and he probably felt, "It doesn't hurt; we can try." And whether he knew much about—I think he knew about Genentech, because he said, "What has been cloned before is too small, is smaller than t-PA, and I'm sure it'd be impossible." I believe there were posters, I remember this very distinctly, and I think this was at this meeting—I'm positive, because it couldn't have happened after—that I was walking around these posters, and so everybody knew I was from Genentech, and a guy walked up to me and said, "Oh, so you're from Genentech," and I said, "Yeah." He said, "You're interested in—I see you've been talking to Desiré—cloning t-PA." He said, "If we thought that it could have been done, we would have done it years ago." I'll never forget his words, and I just thought—he was a famous guy, I can't remember his name, but—

Hughes: Was he an academic?

Pennica: He was an academic, yes. So he said, "If we thought that it was possible, we would have done it years ago." [laughs] Really?! So, I said, "Well, can't hurt to try." So, certain words, I'll just always remember.

Hughes: It doesn't sound to me as though the received word, when it's contrary to where you want to get, slows you down much.

Pennica: Right, exactly.

Hughes: That's about the second or third episode that you've described, where you were told, "No," and you went on.

Pennica: Right, right. Exactly. You don't listen to people.

Hughes: Where did you get that? Where did that idea come from?

Pennica: Who knows? Sicilian, strong-willed background, I don't know—I just [pause] you know, I try to tell my kids—my kids meaning the people who work for me, because I don't have children—I try to instill in them the same sort of enthusiasm, and that's how I hire them, based on whether I see a spark in their eyes when I'm talking to them, because if I don't, I'm not interested. And most of the guys say, "Oh, I can't wait to work in your lab!" Great, okay, fine, you're hired. [laughs] So I instill that in them. I've had people at work say, "Oh, that's never going to work." You don't know until you try. A lot of people leave science because it's very frustrating—it is a painstaking, frustrating experience. You have to have a lot of tolerance for failure. But that one success is just unbelievable. I would get excited about little successes. That's what I think Paul Cohen instilled in me, that every little experiment builds on the next, and you learn something from it. That you can get excited about a little progress. For example, if today I add ten nanomolar magnesium in an experiment and it doesn't work, then you try twenty. And then you try thirty, until it does work, or you change something else. To me, that was always exciting. Many times an experiment didn't work at all, but I didn't give up. That's the way I approach all experiments.

But I think it was innate, I didn't say, "Oh, I've got to convey to them that I'm not going to give up." It was just my positive attitude, I just said, "Oh, sure we can do it!" Never having cloned anything in my life, I had no clue whether we could do it or not. So, Desiré decided to work with us, and when I got back I said, "Look, I met this guy, by accident," and Herb Boyer said, "Nobody could have done it but you, Diane." People at Genentech said, "If you were male, they probably would have kicked you out." They didn't ask me to leave that pre-conference session, because, they told me later, they thought I was one of the scientists' daughters, waiting patiently in the back of the room for her dad.

Hughes: Isn't that something.

Pennica: And that's why they didn't say, "Please leave, this is a private meeting." So I was able to stay there long enough, and I didn't seem threatening to them. I think that was probably

the key. [laughs] You know, I wasn't a spy, I wasn't a threat, and I was able to sit there long enough to hear a lot. I was just in the right place at the right time.

Hughes: Right time, that's for sure. Well, then what happened, because now you were on a much different track, I mean, what did you do about the urokinase?

Pennica: Well, can we—

Hughes: Yes. [tape interruption]

Pennica: So you asked about urokinase.

Hughes: Yes.

Pennica: And how did this put a spin on that? Well, the two projects were very similar, because they were similar molecules, but the advantage of t-PA was that it supposedly bound stronger to fibrin whereas urokinase was more non-specific. So if you have something that specifically dissolves fibrin which makes up a blood clot, it's less likely to do damage in your body somewhere else. Because your body normally is forming blood clots and dissolving blood clots, and there's a balance. When it gets out of balance you have problems. If you have too much dissolving, you have bleeding, and you can have hemorrhaging; if you have too little dissolving of the blood clots, you will form a blood clot. So you form micro-blood clots all the time. When you exercise, if you run or jog or do vigorous excercise, you make more t-PA in your body, and it keeps your arteries clear. That's been known, they've measured t-PA levels in your blood, and the levels go up. So, they thought it was better because urokinase was very non-specific, and it would more likely do damage in your body, so there was an advantage there.

Well, they sent me to this meeting to find out about this molecule, but Bob Swanson was very interested in making sure we honored the Grünenthal contract, and he didn't want me to take time to work on t-PA exclusively. He said, "I don't want you spending so much time on t-PA, or much time." And I said, "But I can learn something. If I do an experiment, and I find it can be applied to urokinase, this is worthwhile." I didn't think it would be an issue because it's very frustrating to work on just one project, because you can hit roadblocks and never go anywhere. And I said, "I'll make sure they both move forward." But he wasn't too happy about it. But I did it anyway; I worked on t-PA because I had made a promise to Desiré that we would do this. I didn't want to let him down, and I thought that this could be something good because he had said that t-PA dissolves blood clots, and there was potential. So, we got all the reagents from him to try it. But I think Bob might have been happier if I had done the urokinase project, shown I could get that to work, then done t-PA. But I did them side-by-side, and t-PA went faster.

Hughes: How does Herb Heyneker fit into this? Because you're still in his lab, aren't you, at this point?

Pennica: Yes. I'm still in his lab. He was happy about it. I mean, you know, the harder I worked, the better. He was another very enthusiastic guy, he always had a spark in his eye. I've been very lucky: There are so many people in science who have terrible Ph.D. advisors, terrible graduate school experiences. I have been so fortunate because everybody I've

been involved with has been excited about science. But there's some dull people in science. I've met a lot of them. [laughs] And I'm saying, "Oh God, I'm glad I don't have to work for him!" Or her, or whatever. Herb was always saying, "This is great, this is exciting!"

Hughes: Was he considering that the urokinase and the t-PA were yours? He wasn't directly working on either project?

Pennica: No, he was more an administrator; he didn't work exclusively in the lab, but he was working on growth hormone at the time, I think, growth hormone and insulin. So these were my projects, and Bill Holmes and I were working on both of them at the time.

Hughes: How did the division of labor go there?

Pennica: This eventually split us up; I eventually left Herb's lab because Bill and I just couldn't get along. It was just a conflict of—a battle of wills, you know. Bill Holmes was doing the cloning part of it, I was doing the RNA part, and I wanted things to go faster. He was probably doing everything right, but I thought I could do it better—I don't know why, I just thought I could do it better. He got upset, and I got mad, and I said, "I want to try this," and Herb says, "Oh, I just think it's funny you two guys are fighting!" Well, to me it was very upsetting because I wanted harmony, and I had never been in a situation like this before, and it got so bad that I didn't want to go into the lab any more. It was so upsetting to me. So I went to see Dave and—no, actually, before I went to see Dave, Goeddel came to me—I had had success with doing some aspects of the t-PA project, and he was following it all along, and he said, "Would you try gamma interferon? We're trying to clone gamma interferon." So this was a third project. I said, "Sure, I'll help you out." And I thought, "Why not? I could do it on the weekends." I was working seven days a week at that point. He had people in his lab working on the RNA, but they probably didn't have the expertise that I did. There was a race with people in Switzerland, I believe—I can't remember the names, you probably know.

Hughes: Biogen?

Pennica: Biogen.

Hughes: Charles Weissmann?

Pennica: Weissmann, yes, Weissmann. There was a race, and [pause] Dave tried for about a year to do this. They wanted to extract the RNA, inject the RNA into oocytes—these are frog eggs—take the medium the eggs were sitting in, and put it on an assay and see if they could measure interferon activity. They had been trying that for a long, long time, couldn't get it to work. Dave asked me if I would try to extract the RNA, because he knew that I had experience in it. So I used my famous gels and I separated RNA, like I had done in my graduate school days, and I sliced the gel into different fractions, we had them injected into the oocytes, we got activity, just like that, first try.

Hughes: Oh, really—isn't that amazing. Had the RNA probably degraded in the previous experiments?

Pennica: Probably. Yeah, and I was so meticulous. I was as meticulous as can be, and everything was fanatically done. That's why I didn't have time to go down the hall and find out what everybody else was doing because I was so focused on what I was doing that it worked the first time. Dave then took the RNA after we got activity. He worked non-stop. He took the RNA, he made the cDNA, and cloned it, and that's how we got to be first.

Hughes: There's another intense person.

Pennica: Oh, God. [laughs] I worked for him for thirteen years! Yes, very intense.

Hughes: How did that work, I mean, two intense people in the same lab?

Pennica: I learned a lot from Dave, I learned a lot, so— [laughs]

Hughes: So, he knew then that you could do something.

Pennica: Yes, he was all excited, so when it got to a head between Bill and I, because we were arguing every day, and he was mad, and I was mad. I was so upset, I just went to Dave, and I said, "You know, I can't work there anymore." He said, "You can come work for me!" I took the t-PA project with me, which Herb was upset about, and I said, "You can have urokinase because that's what you started on before I got there, and—"

Hughes: And it still wasn't absolutely clear which was going to turn out to be the better—

Pennica: Exactly.

Hughes: So it wasn't that—

Pennica: No.

Hughes: Well, I should ask you: Was Herb thinking, "Here goes that woman and she's taken the better of the two projects?"

Pennica: I think he might have thought that; he might have, but I don't know what his thought was at the time. He may remember differently, but this is the way it happened. I was so upset, because I loved working in the lab, and I just thought, "This is so upsetting, I can't go in and fight with this guy every day." But Herb thought it was funny, and Dave says, "Oh, you can work in my lab!" I had proven myself already to him. So I said, "No, I'm taking t-PA with me—I got Desiré, I made all the contacts," and I wanted to take t-PA with me, and I stopped working on urokinase at that point. So, I went into Dave's lab, and that's what I worked on a 100 percent for a while.

Hughes: And did it really move faster?

[Tape 2, Side A]

Pennica: Yes, but it did take a long time. No, I worked nonstop for two years, and basically didn't have a life. I worked seven days a week, I worked from eight in the morning till, sometimes, one in the morning, doing experiments. And then rumors kept coming that

other people were working on t-PA. Kabi, Cold Spring Harbor, Genetics Institute were all trying to do the same thing, and that made me work just that much harder because it was a struggle. We had trouble initially trying to identify a true clone, and we were doing these experiments where you had to sequence some of the positive clones that came up on these films, sequence DNA from the clones, and Bill Kohr—I don't know if you've heard his name—

Hughes: Yes, yes.

Pennica: He's one of the inventors on the t-PA patent. He is a brilliant man; he was the head protein chemist on the project, protein sequencer, and without him we couldn't have done this project. He is such a great guy, smart, smart guy, and no ego. He's just brilliant. And he's told me stories that are just wonderful, too. His bosses would say, "Try this, this, and this," and he would ignore them. He said, "If I did what they said, we would not have had the t-PA sequence." So, he's got some great stories, too. He was sequencing the protein, and he would bring me little stretches of the amino acid sequence that we would make probes from. Now, when you sequence something, if the protein is 100 percent pure, then every fragment of sequence that you get is going to be from that protein; but if there's 1 percent contamination of one or more other proteins, you may get a little stretch of protein sequence that's not t-PA. And so you could make a probe to some other protein that we don't know the sequence of, and you're going to be spinning your wheels for a long time, and not get what you want.

And so Bill kept giving me sequences, and I would sort of remember them. I would memorize the sequences of some of these protein fragments. When we were looking for the very first clone, Peter Seeburg was sequencing them at the time, and he would come to my lab, put a piece of paper down, and say, "Nope, those clones aren't t-PA," because he would compare it to the amino acid sequence that Bill Kohr would give me. The computer system was just getting up and running at Genentech, and I think he was doing a lot by hand. Well, one day, he had sequenced a lot of clones that just didn't turn out to be t-PA, and it's very frustrating, it's disappointing and upsetting because the spots would be blazing on the piece of film, and you'd think, "Oh, that's got to be it!" Well, some of those were probably probed with the wrong thing, others may have just been non-specific stickiness on the filter. Then, one day, Peter came and threw some paper down on my desk and said, "Nope, we don't have it," and after he'd left, I looked down, and I had memorized one of the things I saw, the sequence W-E-Y-C-D, I think that's what it was. I said, "Oh, my God, that's one of the sequences that Bill gave me!" I went in to Dave's office, and my hands were shaking, and I said, "I think we have it." So that was the first clone, and he said, "Really?!" And I was shaking, I was so excited, because we had gone through clone after clone. Peter missed it. Either the computer system didn't find it, or he didn't remember, or we didn't have that sequence in the database, I don't know what the reason was, but he missed it. And I just looked down, and I saw that because I had remembered one of the sequences that Bill had given me, and I was so excited.

Then things moved very quickly after that, and again, the best way is to look in my notebooks to see the sequence of events because I can't remember. But Dave was great because he knew everything about cloning, he told me what to do next because he was the expert. He knew what things had to be done. All this was new to me, so it was a learning experience for me. But he knew how to do it—my hands did it, and he was just

telling me, "Try this, try this, this, this, this." And most of the time it worked, but a lot of the time I did five things at once trying to get something to work. He's a smart man, and he knew exactly what needed to be done, but it took a lot, a lot of work to get that first clone. I worked solidly for another five months, seven days a week, to try to get the final piece of it. The first clone we got was missing about a third of the molecule up at the 5-prime end, and we tried so many different things that just did not work—we couldn't get it because we think that maybe the RNA is twisted in a little hairpin. It might make it difficult for the enzymes to get through and make cDNA. We don't know; we'll never know to this day why it was so tough, but we tried a number of things. We ended up getting a genomic clone to probe a library, and again, I learned a lot about how to clone in that stretch of time, but finally got the 5-prime end.

We started writing up a paper, and again, there was another disagreement where I was mad at everybody, because Gordon Vehar went and told Bob Swanson, "I don't think we should publish this paper." And here I had worked for two solid years doing this, and I said, "What do you mean?" We had a policy to publish papers. He said, "Because the competition will have the sequence, and they'll be able to catch up." I was devastated, I was so upset. I went to Bob and I said, "How could you do this?" Gordon was doing assays for t-PA, but he wasn't as—

Hughes: It wasn't his project.

Pennica: It wasn't his project. And I was so upset with him for the longest time. A few weeks later, somebody called me and said that, "We have a paper from Kabi that is a partial clone of t-PA"—they were going to publish it in *PNAS* [*Proceedings of the National Academy of Sciences*], and I was devastated. They said, "We want to know if your paper, because we know you're working on it, have you cloned it yet, have you—" We had cloned it.

Hughes: This was the publisher, now?

Pennica: No, this was a reviewer—he shouldn't have done this, he never should have called me. I don't know who it was, but he said, "If your paper's already in press, I'll reject this paper, I won't accept it." I said, "I have to be honest with you: We haven't submitted it yet," because Genentech was holding it back; I didn't say Genentech was holding it back. I was so upset, and then I called Bob, and I yelled at him. [laughs] I <u>really</u> yelled at him. And he had Human Resources call me, and he said, "Try to calm Diane down." They said, "Why didn't you call us first?" I said, "I don't have a problem with you; I have a problem with Bob!" [laughs]

Hughes: Good for you, good for you.

Pennica: I yelled at him. I said, "Bob, you haven't been working as hard as I have, I've been working seven days a week—I want to publish this stuff." I said, "And a journal editor just called me and said another paper was going to be published—we're going to get scooped." I said, "I know they don't have a full-length clone, but we're going to get scooped." And then they let me submit it to *Nature*, because another paper was coming out.

Hughes: How long was the publication delay, do you think?

Pennica: I don't know, that I can't remember. I just remember calling up Bob and yelling at him. No, I think I did it in person. I was shaking, I was so mad. [pause] He has probably never had anybody yell at him like that. [laughs] I said, "How could you do this? Because we don't want to get scooped." Well, [pause] I don't know, it was so emotionally charged.

Hughes: Did this have anything to do with Swanson's original skepticism or if you could put it that way, about why you should be even concerned with t-PA?

Pennica: I don't think so. I think at that point he knew, because he'd heard about all the rumors of everybody trying to clone t-PA, that it might be a big thing, and that if we published the whole sequence, then anybody in the world could get it.

Hughes: So he was getting it, that this was a hot thing.

Pennica: Yeah, yes. So Gordon convinced him, "Oh, we shouldn't publish this." Oh, I was so mad. I was so mad.

Hughes: And it was published in *Science*?

Pennica: *Nature*. Kabi did publish theirs, but it was a partial clone, so it wasn't the full-length clone.

Hughes: So you got the credit that you deserved?

Pennica: Yes, yes. And the Kabi guys—I actually met them—they came to Genentech, they were in town one day, and they said to me, "How did you do it? It almost killed us!" I said, "It almost killed me, too." I said, "But I probably worked harder than you guys." I said, "It was the toughest thing I've ever worked on, and the fact that I heard, that there was rumors that you guys were working on it too, made me work so much harder." And I said, "I'm not surprised you didn't get a full-length clone, because it took me forever to get that final bit."

Hughes: So they'd had the final problem with that final end.

Pennica: They had a problem as well. You know, I think we scared a lot of people because I think they thought that we had an army of people working on it. I said, "No, it was just me doing the cloning at that point." There were other people—Bill Kohr was instrumental, Gordon was doing assays, Dave was the director—he was the one giving the instructions.

Hughes: And then what happened? Did you have anything to do with the development, the scale-up, any of that part?

Pennica: No, no. I did not. I expressed it in *E. coli*, I expressed it in mammalian cells, and then it had a mind of its own. I mean, the whole project was taken over by other people.

Hughes: I see.

Pennica: And I moved on to the next thing.

Hughes: Now, what about the fact that Genentech had this mammalian cell expression system? We're talking now very early eighties, right? Do other people have mammalian expression systems, or is this giving Genentech an advantage, that you already have this system in place? Or was it in place for t-PA?

Pennica: I think they must have done some mammalian cell expression, but I don't know, I really can't—they used CHO cells and 293 cells—

Hughes: I think interferon.

Pennica: Interferon probably was, but I really don't know, at the time. One thing that I forgot to mention, that was another high point, is after the cloning, I submitted an abstract to a meeting to give the talk on the cloning of t-PA, in Switzerland? I can't remember where it was. It was going to be the announcement. I had to write an abstract that was very vague—we're trying to do this, this is how we're trying to do it. I couldn't say anything, and our lawyers said, "No, you can't say it because it would be like a public announcement."

Hughes: Oh, absolutely. So the patent hadn't been filed yet?

Pennica: The patent hadn't been filed? No, the patent had been filed, but not released, so it's not public knowledge that we had done this. So, I had to make a very vague abstract. The meeting accepted it but they put me as the last speaker on the last day; there was five days of talks. I was the talk right before noon, and then there was a clinical session, which was not science stuff. And I said, "Why'd you put me on last?" I said, "I hate being last." One of the guys I had met at that first meeting in Malmo said, "Because we don't know what you're going to talk about, and you didn't give any information." I said, "Well, I can't give any information—I guess you'll see when I get up there and talk whether it's of interest." I was so excited because I had cloned t-PA, and Desiré was there at the meeting, and he knew that we had it. I'll bet that he told people, but I don't know for sure. I got up, and I gave my talk, and they set timers when you give a talk, usually at meetings, because they don't want people going over. Halfway through my talk, I had just flashed up the structure of t-PA, with all the kringles and all the dots, I had put on a board, the timer goes off. I looked at the audience, I said, "Should I stop?" The whole audience says, "No!" [laughs] Everybody started to laugh, and I continued. At the end of my talk, they gave me a standing ovation, which is unheard of at any scientific meeting. I couldn't believe it. Somebody came up and said, "Are you one of the marketing people? You gave such a great talk." I said, "No, I'm the scientist who did the work!" They said, "But you were so polished." I said, "Because I practiced for a month to give it." But I practice and practice, because I'm so nervous, that they thought a non-science person gave this talk.

Hughes: Isn't that amazing?

Pennica: But that was really a high point.

Hughes: So people did come, probably because Desiré had said, "You'd better get there."

Pennica: Probably, but the room was probably three hundred people, and one guy had put up a—I think from Genetics Institute, which made me so angry—he put up a camera in the

aisle, and started filming it. One of the guys—it might have been Elliot Grossbard—who went up to him, and said, "What are you doing?" And he said, "I'm filming." He took pictures of every one of my slides, which was pretty [laughs] lousy.

Hughes: Yeah, I'm surprised that's even allowed.

Pennica: Well, they stopped that after, but he took pictures of all my slides. Then somebody came up to me and said, "Well, how are you expressing it? Do you have expression in yeast, do you have expression in *E. coli*, do you have expression in mammalian cells?" And I felt like I was being pumped for information.

So right when I gave my talk, Genentech issued a press release that we had cloned t-PA, at the exact same time. That was pretty exciting.

Hughes: I can imagine.

Pennica: It was too bad that my talk was on the last day because I would have liked to talk to other people at the meeting. Because, if you're first, people come up to you and talk to you throughout the rest of the week because they want to know more about what you've presented. The organizers just said, "Well, we didn't know you had anything important to say."

Hughes: What is Desiré Collen like as a personality?

Pennica: Oh, he's great; he's a teddy bear! [laughs] He was always sweet; every time he came here, he'd bring me a little box of Belgian chocolates. He was excited, too, about the work—he got the equivalent of the Nobel Prize in Belgium for the t-PA work.

Hughes: Is that so?

Pennica: Yeah. I don't know what the name of the prize is, but it's the equivalent. He now has a whole institute, I think, that he runs, and he's become very famous over there. So, he's great.

Hughes: Do you know the history of how he became interested in t-PA?

Pennica: No, I don't. That's a good question. Was it fibrinolysis? Maybe he had been studying fibrinolysis his whole life, and he isolated a substance because he wanted to try to dissolve blood clots. I don't know how he became interested. They didn't know for a long, long time what in your body dissolved blood clots, or even if there was such a thing. I have a series of slides, that, if we are going to get together to talk again, that I can show you, that details the history of this, which is so exciting—you actually read it, you read part of it in that book chapter—about how they discovered that it was actually worth something.

Hughes: I know Marsa gives credit to Peter Rentrop?

Pennica: Yes, right.

Hughes: Is that the way you pronounce his name?

Pennica: Yes. But I did a talk detailing the history of it—but whether Desiré—he was probably looking for things that dissolved blood clots because he found that this melanoma cell line produced a substance that would dissolve blood clots and then subsequently tested it on a woman who had a deep-vein thrombosis.

Hughes: And as so often is the case, I saw some parallels with the interferon story, that people have known about these substances for decades, but because there is so little of it.

Pennica: Right.

Hughes: It holds the science back.

Pennica: That's right. If you can't get pure protein, you can't clone it. Well, you can now because if you have an activity, you can. They're called expression-cloning projects, but back then, our techniques were so archaic that I can't even imagine trying to do some of the things that we did back then. It takes a week now to do things that took a year back then.

Hughes: As we know again from the Marsa book, there was a lot of controversy, particularly in clinical trial and FDA approval stages. Were you watching that? Here was your substance, moving slowly and with considerable setbacks toward actual clinical use.

Pennica: I watched it briefly, but again, I was so entrenched in my next project, which was TNF [tumor necrosis factor], that I was almost oblivious to what was happening. I just thought, "Well, I hope this works," and I kept hearing things that were going on but didn't follow it that closely because I was, again, working on stuff on the next project. That was just my intensity; I can't think of anything else. [laughs]

Hughes: Shall we save TNF for next time?

Pennica: Sure, yes.

Hughes: Let me just—do you have a few more minutes?

Pennica: Oh, yeah, of course.

Hughes: I do feel a little uneasy, since I don't ask the men this—

Pennica: Oh no! [laughs]

Hughes: But I think it's relevant to ask you how it was to be a young woman in what seems to me to have been not only a really predominantly male organization, but also, in the early days, somebody has even described it to me as kind of like a fraternity house, you know.

Pennica: Yes.

Hughes: [laughs] So how was that?

Pennica: Good and bad, in a way, because I didn't feel part of a group, the gang. I just didn't. But in a way it didn't matter, because it made me focus more, and I [pause]—you know, I

think anyone can succeed despite the fact of being a woman. I think it's tough because there are a lot of things that have happened that I feel are not as fair as they could have been, but I have been successful and done a lot of things because I keep my nose to the grindstone, and I try not to get upset about a lot of things. Luckily I stayed when it got so uncomfortable in the lab, when Bill and I kept disagreeing—Bill Holmes—but I'm glad I stayed because I don't know what I would have done. I would have gone to another company, I guess, but it was just too much fun here.

Hughes: Do you feel that because you were a woman you had an extra burden of proving yourself?

Pennica: I think so. I think that's very true. But I also think I got into that meeting because I am a woman.

Hughes: Yes! [laughs]

Pennica: They said, "If you were a guy, we would have kicked you out, because we would have thought you didn't belong here."

Hughes: It cuts both ways, doesn't it?

Pennica: Right, yes. It's been tough at times, but it's—

Hughes: Do you see any difference in—well, this is probably an impossible question—do you see any difference in the way you think about and actually do science because you are a woman?

Pennica: Not at all.

Hughes: No.

Pennica: No. I don't think that makes a difference at all because my style is probably different than any other style. I'm more fanatic than most about doing everything perfectly and that probably increases your chances of success. A lot of people say, "Oh yeah, I tried it this way today, the next day, tomorrow, I'll do it a different way." But if you don't do an experiment the same way day after day, and you know what works, don't change anything. This is what I drilled into my people, but I don't think it has anything to do with being male or female. It's just your personality. I always loved the lab work, I thought it was so much fun, I always got excited about it. But that's not a male/female thing because I think there are men who—a colleague of mine, Michael Marletta, who is now at UC Berkeley, he won the MacArthur Genius Award—he went to Fredonia State. He was in the same classes with Dr. Fox, and all the professors I had, and he just recently this year got in touch with me. I hadn't seen him in twenty years.

Hughes: How funny.

Pennica: And he won this award. He has a spark, he is another guy that works intensely at science. You just can't be set back, because there are a lot of problems—but male/female? No, I don't think that's—I think that was an easy question!

Hughes: [laughs] Do you still do hands-on science?

Pennica: Not any more. I have two people working for me and it's hard because I think I want to have a life now, and I didn't before, because science is so demanding. It's very tough mentoring people and working in the lab at the same time. Because when I'm in the lab, I don't want to talk to anybody; I don't even want to be interrupted for a second because you can be distracted too easily. If you're only supposed to spin something for thirty seconds, you can ruin an experiment if somebody comes and talks to you and you spin it longer. So I was probably thought of as antisocial, because I didn't walk around, because I paid attention so carefully. I resisted for a long time to get somebody to work for me. Dave would say, "You've got to get somebody to work for you." I don't want anybody, I don't want anybody. I thought it was too tough to teach somebody and work at the same time. And it is. I usually got kids right out of college, who wanted to go to medical school, wanted to go on to graduate work, because I knew they would be ambitious. But then I had to start teaching them, "Here's how you pull a filter, hold a pipette this way." I thought, "How can I do work in the lab, because they would be asking me questions every ten minutes." And so I slowly, slowly phased out of the lab and now I don't work in there anymore. But I miss it.

Hughes: I bet you do.

Pennica: It's just different.

Hughes: When did you marry, and is that one of the reasons that you began to cut back?

Pennica: No, I am now divorced, and I'm very, very happy. I'm very happy with my life right now. I got married in 1990.

Hughes: So after all the t-PA.

Pennica: Right, after all that, because I was too busy before. It was just too busy. Yeah, I don't know if I could—there's a lot of women who can do it all, have kids, have a full-time career, have a good marriage, and I didn't. I was 100 percent focused on work. Now I really want to have a life. I still love the science, and get excited about it, but I can't work here a hundred hours a week like I used to. [laughter] It was too much.

Hughes: That seems reasonable!

Pennica: Right. My mother died very early, she was fifty-nine, she died of colon cancer, and [pause] life's too short not to have fun, and I just hadn't had fun for a long time. I had fun in science, I will never regret that, but—one thing I didn't tell you about, but this was in the book. This is a Christmas card that I got from Mike Blum—no, that's not in that book. That's different, that was about the first heart-attack patient I met. Then I got Christmas cards and other letters. I have things tacked up all over my wall from patients. That's only a handful of the things that I've gotten.

Hughes: And what is the Mike Blum?

Pennica: He had a heart attack, and he got treated with t-PA, and I just got this random card from him. The card says: "Dear Dr. Pennica, Thanks for helping to save my life. Mike

Blum." Boy, when I have a bad day, or I think I'm not being treated well, I look at that, and say, "Well, there's no other guys who have that tacked up on their wall."

Hughes: Well, let's end with that story of meeting the patient. Is it really true that it was the day of the party, because we didn't talk about the party, either, the celebration—?

Pennica: No, it wasn't the day of the party, I don't think. I don't know why he came here, I think he wanted to see the company that made t-PA. Steve Birnbaum came to Genentech, and I was in the hall, walking very fast like I always do, trying to get to the lab, or someplace. One of the marketing guys said, "Oh, Diane, I want you to meet somebody." I said, "Sure." Again, I was always in a hurry to get to the lab. He said, "This is Steve Birnbaum. He is the first heart-attack patient to be treated with t-PA." I said, "Oh my God!" Steve didn't know who I was, and he said, "This is Diane Pennica. She's the woman who cloned t-PA." And Steve immediately just grabbed me and hugged me, and said, "Thank you! Your drug saved my life." Unbelievable.

Hughes: What an emotional—

Pennica: Oh, it was great, absolutely great. That one experience was worth any aggravation that I've suffered [laughs] over the years.

Hughes: You've spoken a lot about your passion for the science. Was this kind of icing on the cake, the fact that, yes, the science is really exciting, but look what it does for people?

Pennica: Right, and I never thought that I would ever meet somebody—clinicians, M.D.s meet patients all the time, they're always getting thank yous, and things like that. As a researcher, you never think that you're going to meet a patient, ever. I feel very fortunate because most people who work in science are never going to get that opportunity. They're going to work on things that may never translate into something that hits the clinic, and to have something like that happen is incredible. Somebody came into my office last week and said, "I want to tell you that my uncle had a stroke, and they gave him t-PA, and he is alive and well, and he wanted me to come thank you." And I thought, "Oh my God!" So still now—

Hughes: It's still happening.

Pennica: When t-PA was announced, my small hometown, Fredonia, had all these honors for me. I got the Service to Humanity Award, I got asked to be a commencement speaker there, I got lots of accolades. Then people from Fredonia would send me letters saying their mother had a heart attack or "I had a stroke," whatever. So I've gotten stuff like that, too. It's really very rewarding.

Hughes: When you were doing the science so intensely, were you thinking in the back of your mind about clinical application?

Pennica: Not really. You know, I sort of knew what it could be useful for, but never thought it would ever have an impact like this because I didn't know our capabilities at the time. I didn't know we had the facilities to actually take something all the way to clinical practice.

Clearly, this is an amazing company, because it's done so much already, and I'm very honored to be a part of it. I am very fortunate that things have happened that—who knows why they've happened. Because I'm basically an unbelievably shy person, I hate giving talks; I really hate it. And that's the only way you're going to get well known. Well, I gave a lot of t-PA talks, but it's a struggle for me every time. To have something like this happen, you know, "We want you to give a commencement speech"— oh my God! Two thousand people! [laughs] But I go and do it. I got asked to give a talk at Vanderbilt University to five hundred graduate students and postdocs, and it was only a fifteen-minute thing. I was terrified. This was just last year, and yet I did it.

[End of session]

**INTERVIEW 2: JULY 23, 2003**
[Tape 3, Side A]

Hughes: Today we're going to start with tumor necrosis factor [TNF], which I'm going to leave to you pretty much to tell the story, since I don't know much about it.

Pennica: So, tumor necrosis factor, which we call TNF, was first described in 1975 by a scientist named Carswell, as an activity in the serum of mice that, if you put it in vitro it would kill cells, or in vivo, it would shrink tumors. We decided that that was something worthwhile pursuing because it could be a cancer therapeutic. So, in 1983, I believe, again I'll have to check that date in my notebooks, we decided to tackle this as a project. We found a cell line, much as we did with t-PA, that produced TNF. You have to find a cell line or some tissue that makes a lot of the protein that you're interested in, so you can isolate the protein, determine the amino acid sequence by conventional methods and make a probe to a portion of that sequence. You could then probe a library to see if one of those clones has a piece of the DNA that encodes TNF. So that's the strategy we used for t-PA, and we used a similar strategy for TNF.

We first looked for a cell line. We took a number of different cell populations and assayed them for TNF activity. In a sense, we looked for cell killing, and we found that a cell line called HL-60, a promyelocytic cell, produced activity. So we used those cells, isolated some protein by conventional methods and got a preliminary protein sequence. From that protein sequence we made a probe, we made a library, and we found some clones. We got a sequence that, when we expressed it in *E. coli*, it did kill cells in vitro. We injected mice with cells that made tumors, and found this protein was able to shrink the tumors in these mice, which was very exciting. Unfortunately, this never went on to become a drug because it had such potent activity and side effects, so we didn't pursue this any further at that point.

Hughes: Did it get as far as human clinical trials?

Pennica: You know, I think it did, but again, I am so out of that loop. That's something that I could check. I bet it did.

Hughes: Now, who's the "we" involved in this work?

Pennica: Again, the same people who were involved in—the major players in the t-PA story: Bill Kohr, who was instrumental in determining the protein sequence of the isolated protein; and Dave Goeddel, again, with his wisdom, advising us on the best cloning strategy; Glenn Nedwin was involved; Joel Hayflick, Peter Seeburg, Rick Derynck, Michael Palladino, and Bart Aggarwal, they all made contributions. But I think the core was, again, the same people who did work on the t-PA project.

Hughes: Now, are those cell lines you mentioned already in Genentech's possession?

Pennica: I think they were. We got these from the American Type Culture Collection, and we just screened a number of them, including peripheral blood leukocytes, for activity. We fractionated PBLs because they contain a number of different cell types. So, we were successful, and we were the first, once again, to publish the cloning of TNF, which was great.

Hughes: Who were your competitors?

Pennica: I think there were competitors in Europe. Charles Weissmann I think was trying to do the same thing. Dave was always anxious to beat him. I think we beat Charles Weissmann on the interferon cloning as well. I'm not sure he was working on TNF, but there was another group who published the cloning of TNF many, many months later in *Science*. I couldn't understand this, because the journal should have said, "Well, this has already been done," but they published it anyway. I can't remember the name of that group, but I was upset, because I went to Dave and said, "How could the journal *Science* let this be published? We already did it; they published the same sequence. They just went about it using a different strategy." We did have competition, but we were first. So that was great, very exciting.

Hughes: Who is responsible or how does it usually happen that a project like this gets off the ground? Is somebody reading the literature and comes upon the work that you cited in the case of tumor necrosis factor and said, "Well, maybe this is something that Genentech should be developing?"

Pennica: Yes. At that time, they listened to anybody who had a great idea. I believe it was Rick Derynck who said, "This is something that we should pursue: There's this activity. They discovered that this stuff was in the serum of mice; it's probably something we can clone." If it's not a single protein that's killing these tumors but a combination of many proteins, then it's going to be impossible to clone. But I think Rick Derynck was the one who came up with the idea, although he wasn't involved in the cloning aspect of it. So he gets credit for that idea, and at that point we just decided to work on it.

Hughes: Did Swanson, or some of the other executives, have to give it an okay?

Pennica: I believe so; I think—

Hughes: The scientists just couldn't take off, and begin a project.

Pennica: Right. But the fact that it was cancer-related, I think that was enough to warrant it being pursued, and Dave Goeddel is very convincing, and he's usually right, 99 percent of the time—probably a hundred, he'll say! This was something worth doing, and in hindsight, it certainly was.

Hughes: Tell me about that, tell me how it became useful.

Pennica: Again, I don't know how far it got in clinical trials, but that's documented somewhere. But right now, what's important about this is: Without the cloning of TNF, the drug Enbrel would never have been developed—that's for arthritis—because Enbrel uses the receptor for TNF to block TNF activity. The receptor was subsequently cloned also at Genentech, as the target for inhibition by this drug. Enbrel could not have been developed if TNF had not been cloned. That's pretty exciting. I get satisfaction knowing that I was at least part of it.

Hughes: Were you involved in any way with the cloning of the receptor?

Pennica: Yes, I was, and what's upsetting to me is that I was going to put my name on the paper—Dave put my name on the publication because I did probably two years worth of work on it. It was very, very difficult, but in the end, none of the data that I did, even though I worked for two years, went into the paper, so I felt that I should take my name off. I'm very upset that I did that now because people get on publications for doing nothing. And that's upsetting. Dave said, "Oh, you shouldn't worry about what anybody else thinks," and I was worried that they would say, "Well, none of Diane's data's in the paper." He said, "But you worked, and your data helped to get this far." I could kick myself. [laughs] But it's just a publication—but I should have been on that paper and I took my name off. I should've because I have notebooks filled with data on trying to clone the receptor. It's not that I didn't work very hard on it; I just felt guilty because none of my figures or anything else went into the paper.

Hughes: I'm assuming that in the progression of a project that areas that prove not to be productive still contribute to the project.

Pennica: Absolutely.

Hughes: Because you know that then, this is not the way to go.

Pennica: I was naïve, I was naïve in thinking that—I was worried about what all the other authors would think. Silly me. [laughs]

Hughes: Is there usually a lot of discussion around who should be authors and how they should be ranked?

Pennica: Yes, a lot of discussion, and it gives people a lot of anguish and heartache for people they want to put on that they don't, or vice versa. Other people who think they've contributed a lot sometimes don't get on. It's a tough call. My strategy has usually been: Put everybody on the paper who has helped. Because it makes them feel terrific, they'll want to help you again. As a result, I've really been fortunate because a lot of people at Genentech say, "Oh, I'm going to help Diane because she put me on this paper and this paper and this paper," and they usually do make a substantial contribution, so I have no problem. But in the beginning, there were some papers that I thought, "Why is this person included on this publication?" because he or she did not do enough to warrant it. That's why I felt that I should take my name off the TNF receptor paper because none of my data went in, even though I worked maybe harder than some of the authors, but hindsight's 20/20! [laughs]

Hughes: Yes, yes, it definitely is.

Pennica: And Dave convinced me, he said, "Oh, don't worry about what anybody else thinks." He said, "You should keep on it," but I said, "No, I don't want to be."

Hughes: Does Genentech in general follow what I believe to be the norm in that the last author is usually the lab in which the work was primarily done, and the first author is the person who did the most hands-on work?

Pennica: Yes, right.

Hughes: So those two are probably not terribly difficult to decide, it's just the authors in between and how they should be listed.

Pennica: In general, yes, that's true. Yes, because it was always nice to see "Pennica, et al." Because when you reference, it's the first author, usually. Or if somebody in a journal is referencing the paper, they may say, "Goeddel's lab," because he would be the senior author. But in this case, different from t-PA, Dave went on to give all the talks on TNF. He announced it in a conference. I did the t-PA stuff; he announced the TNF work even though I did the majority of the work here. [pause]

So anyway, it was another exciting thing because we were first once again, and that was the important thing and that was very important to Dave, and it was important to me, too. I liked being first; I liked to be the first author on a paper because I've been beaten before. I've worked on things that I've been scooped on. You open up a journal, and you've worked for a year, a year and a half on a project and find out they've cloned exactly what you're working on. It's so depressing because you could publish it months later, like they did for TNF, but it doesn't have the same impact.

Hughes: Do you think that being first was a stronger drive at Genentech than most other organizations?

Pennica: Well, I think, for patent reasons, it was important to be first. I never thought of it that way because I didn't know at the time how patents protect you. But scientifically you wanted to be first, because, again, nobody remembers number two! [laughs]

Hughes: Exactly.

Pennica: I've gone to meetings, and they would say, "You're the woman who cloned t-PA, you're the woman who cloned TNF, you're the woman who cloned p53." It's a great feeling.

Hughes: I bet. Well, tell me a little bit about the patent process from a scientist's standpoint. I mean, when you do do something, and you know you've succeeded, what happens then in terms of the intellectual property protection?

Pennica: Well, the lawyers are contacted, and now—

Hughes: Would you do that if you're the lead scientist on the project?

Pennica: Yes. This all happened in the background, usually. For TNF and t-PA, the lawyers were busy working on it, and I was busy working in the lab so I just conveyed what data I had to them, but I was not involved in writing the patent, or anything else. So I considered it more of an annoyance, because they were taking up time away from the lab.

Hughes: Well, maybe let's use TNF, then, as sort of the model because there you must have been directly involved in writing up the patents, weren't you?

Pennica: No, I wasn't, and I don't think I'm even on the TNF patent.

Hughes: Not TNF, I meant t-PA. Describe what that entailed.

Pennica: The lawyers would come to you and ask you for the sequence; they would ask you for the protocols, the methods, exactly how you did it, what cell lines you'd used, what antibodies, step by step.

Hughes: Now, was this Tom Kiley?

Pennica: Tom Kiley, yes. He was nice to work with; he was great. I think he was excited about all this, too.

Hughes: Do you discuss kind of a legal strategy? I mean, how to present this, or is that in the bailiwick of the attorneys themselves?

Pennica: The attorneys do that.

Hughes: So you're just giving the scientific data.

Pennica: Right, and I think they were learning as they went along because this was new territory. I don't know how many molecules had been patented that had been cloned before. Somebody may have told you that in some of the interviews, what the status of that was, but I don't know how many previously had been cloned, and you have to think of: What if you can find another use for it? Can somebody else get a patent because they claim that this molecule can be useful for strokes, and we don't put that in our patents? That's something that Genentech had to learn, or maybe they were very savvy about it, I don't know, it was all in the background. They just said, "Diane, give me this data, give me that data." And I did.

Hughes: So it sounds as though you appeared at the right moment, but then very quickly went back to your lab. [laughs]

Pennica: Yes, yes. I think I told you this in the hallway, maybe I didn't; I don't know if I told you this. Maybe I was telling my RA [research assistant], I can't remember. But, at one point, when I was working on t-PA, lawyers from London came—did I tell you this story?

Hughes: Not on tape.

Pennica: I was working in the lab. Tom Kiley hadn't called me in advance, and he said, "Diane, we have the lawyers from London here, we need you to talk to them." And I said, "I can't, I'm extracting RNA." He said, "What do you mean, you can't?" I said, "I cannot leave the lab, there's no way I'm leaving." Because you have to start an experiment four days in advance to get the cells ready, I wasn't going to leave. They couldn't believe it, that I told them no. He said, "They're only going to be here for a day." I said, "I don't care. I'm not going to ruin my experiment." So I'll never forget that; I was just telling them my experiments were more important than the lawyers from London. It's funny now, but I was annoyed at the time. I was very upset because I was torn, but I wasn't going to let my experiment mess up.

Hughes: Four days down the drain.

Pennica: Right. No, it's too hard. "What do you mean, you can't come?" "I can't come." Here's this little woman telling the lawyers that she can't show up. But they never gave me any advance notice that they wanted me to talk to them. If they had, I could have planned my experiments differently.

Hughes: Well, it probably came as quite a surprise to them. Well, if that's enough on TNF, I believe what was also going on at the same time was, you were working on p53.

Pennica: Yes.

Hughes: Do you want to tell a little bit about that molecule?

Pennica: Yes. I'd like to read a little bit from a review that came out when this molecule was nominated in 1993 as "Molecule of the Year." Because when we were approached by Arnie Levine to clone this, back in 1983. The paper that we published was in 1984, and Art [Levinson] knew Arnie Levine; Art did a postdoc in Arnie Levine's lab, and Arnie felt that we were the best at cloning things, so he came to us. Dave said, "Do you want to do a side project?" And I said, "Sure." So there's a molecule called p53. I said, "What's that?" But, I'll read a little bit from this.

Hughes: That's fine.

Pennica: Because it's an interesting story. It says, "Back in 1979, when p53 was discovered, nobody would have nominated it for 'Molecule of the Year' or even of the month. First identified in association with tumor-causing viruses that don't cause cancer in humans, this fifty-three kilodalton protein was simply one molecule among many, a discovery that might or might not be important in cancer. Now, in a classic parable of how basic research can have a profound impact on human disease, this dark horse molecule is blazing a bright trail in cancer research. Found in both inherited and spontaneous cancers, p53 is to date the most commonly mutated gene in human tumors and is one of the star members of the tumor-suppressor gene family. Of the six and a half million people diagnosed with cancer every year world wide, half have p53 mutations in their tumors." Which I think is amazing, and nobody knew that at the time when we started working on this project, back in 1983. "Sometimes called the 'guardian of the genome,' it's a leader in the body's anti-tumor army, helping to coordinate a complex system of responses to the DNA damage that might otherwise lead to cancer." So if you get hit by sunlight, for instance, or radiation, or tobacco smoke, your DNA will get mutated, and p53's function seems to be to suppress the tumor, the mutation effect of what these damaging agents might do. "Like an emergency brake, wild-type p53 can halt cell growth, and sometimes send a cell into a programmed spiral of death." Meaning, if the cell's too badly damaged, instead of having that cell grow uncontrollably, p53 will kill it, so it can't go on to form a tumor, which I think is amazing. So normally, it would act as a tumor suppressor, but if the cell is too far gone, it says, "Kill this cell." "Ironically, for the first ten years after it was discovered, it languished in the backwaters of research; it was thought to act only as an oncogene, a gene that actively promotes tumor growth because scientists were inadvertently working with a mutant form. In 1989, p53's fortunes changed; researchers found a point mutation in p53, and mutant p53 promotes abnormal cell growth, the wild-type gene suppresses tumors. Suddenly, p53 became a hot ticket in cancer research."

When we cloned it in 1984, Arnie told me later, this was the first wild-type p53 gene that was known to be published. There was another group, Moshe Oren, who published p53 cloning, but I believe he published the mutant form, we published the wild-type. It was only a few months before, or it might have been a year before, I can't remember.

So just to tell you a little bit more, more than fifty-one types of human tumors carry p53 mutations, 70 percent of colon cancers, 50 percent of lung cancers, 40 percent of breast cancers carry p53 mutations. That's why it's become such an amazing molecule to study. At the time that we were cloning this, I had no idea that this would be such an important protein.

Hughes: That's interesting, isn't it? Because you're literally down at the test tube level, to use a metaphor, as is of course appropriate; this must happen in many cases when there's not too much known about this molecule, and then this whole different world opens up during the clinical trials, or maybe before, I don't know exactly.

Pennica: This was before, just because they're studying tumors, and they're trying to figure out what's going on. That's why when I have people working for me in the lab, I try to point out the fact that even though you're working on something today, ten years down the road this could be another p53—you don't have a clue because people don't know enough about it. That's one of the reasons that I send out clones to everybody who requests them, all around the world, because when we stop a project, even if it's not going any further at Genentech, somebody else may discover something about this molecule that we don't have the capability of doing, or we are focused on something else. It's left my lab, so I figure, send it out to the whole world, they may find something that's exciting. A lot of people don't have that attitude; they say, "I want to keep everything to myself, it's too much trouble to send out a clone." Well, it is, but I have collaborators all over the world, and they have published a lot of very exciting work, that may be important someday.

Hughes: And does Genentech have no compunctions about your releasing clones, for example?

Pennica: As long as we have patents on them, and we have a good MTA in place, Material Transfer Agreement form, where the university, or whatever group we are working with, signs all the papers that we need to have them sign, then it's not a problem. So I can't send anything out. In the early days we could. Now they've learned that we have to protect ourselves and protect the universities. But I love it when people ask for the clone, because I think, "Great, I'm glad somebody's interested." They think it's important; they think it's interesting. And they're working on some obscure thing that could potentially lead to another therapeutic, which is great. We're not pursuing that angle, so we might as well let someone else study it.

Hughes: Talk a little bit about the actual science, as you were pursuing it with p53. Was it difficult to clone?

Pennica: No, I believe it was relatively easy. [tape interruption]

Hughes: Diane, you were saying off tape that it looks as though the protocol was pretty similar to what you'd use for t-PA and tumor necrosis factor, and you can describe that in a minute, but I'm wondering if, at this time, and now it's about 1984?

Pennica: Probably 1983.

Hughes: In 1983, okay. Is Genentech beginning to lose the advantage it had in being such a whiz at the whole cloning—this and the expression business? Are other companies and groups and universities beginning to catch up?

Pennica: We had competition, clearly, because Genetics Institute, Kabi, Cold Spring Harbor, they were all in the t-PA race to begin with, so they were trying to find the molecules to clone. It was a question of deciding what was the best thing to clone. Now, maybe p53, because it seemed so obscure, wasn't something that was in hot pursuit by anybody. I don't know. But what was known at the time was that Moshe Oren and Arnie Levine had published the 3-prime untranslated region of p53 messenger RNA in 1983, but they couldn't get the full-length clone. Arnie asked Genentech for help in getting the rest of the clone. So we took a cell line that they knew contained p53 messenger RNA. It was the F9 embryonal carcinoma cells, and we had tryptic peptides that were specific for p53, that we knew the amino acid sequence of, and we probed a library made from these F9 cells. So Arnie had tried. He got a little stretch of the 3-prime end, couldn't get the rest of it, so he came to us.

Hughes: And he was in academia?

Pennica: Yes. He was at Stony Brook at the time. Yes, State University of New York at Stony Brook.

Hughes: Yes, I was wondering how much of a difference at this time, 1983, it makes to be in a company such as Genentech, I mean, a biotech company—that's a big point—as opposed to an academic laboratory, because you have people here who are specialized in doing specific things. You are usually involved with the cloning.

Pennica: Yes.

Hughes: But then you have somebody else do the amino acid sequencing, et cetera, et cetera.

Pennica: Right. We have divisions of labor.

Hughes: Right. Divisions of labor. But I would think that you'd have to be a pretty big academic lab in order to have all that expertise in one place.

Pennica: Probably, yes. Although people kept coming to me later at meetings, saying, "We could never compete with Genentech. It's such a powerhouse. You must have a hundred people working on a project." And I said, "Oh, no. Three, four, maybe." They don't realize that we had the best in the world—Dave Goeddel, who knew how to clone and passed on his knowledge to me, and so I got the best teacher. And Bill Kohr, who people outside Genentech had said, "He's the best protein sequencer in the world." So with that in hand, you don't need that many people. You just need to work hard. And I think these outside people were intimidated, thinking, we can't work on this because Genentech's working on it. That's what I got from a lot of academic people, and I said, "Why not?"

[Tape 3, Side B]

Pennica: People would assume they never could compete with us because we had hundreds of people working on a project, but that wasn't the case. We just had a small group who worked like a hundred people.

Hughes: Yes, yes. And who also, as you were pointing out, were in most cases the best in the field.

Pennica: Yes. I think we had the best in the field. Dave knew all the tricks or things to try. In many cases, the things we tried didn't work, but each gene that you work with is different, and that's why you can never predict success, and that's why I think the patents are important. When we were trying to defend these cases in court, the patent attorneys would say, "Well, it's obvious that it can be cloned." And my response to them was, it's not obvious that you would ever succeed. You can try, but it's not obvious that it would work because every molecule is so different. And there's problems with each project that we encountered. So you have to try different strategies. With t-PA, I tried five or six different strategies just to get the 5-prime end. There's not a cookbook that tells you how to do certain things. There's things you can try, but believe me, everything's a struggle.

Hughes: I can imagine.

Pennica: So basically, we published the first wild-type p53 clone, which was quite exciting, given the fact that I had people saying, "Why are you working on p53? What is p53?" And then later, I would say, "Molecule of the Year," because we didn't know at the time.

Hughes: Do you want to bring home the importance of the fact that you were working on the wild-type? Is it just simply that most people were working on a mutant?

Pennica: The fact that most people were working on a mutant, they thought it was just involved in tumor growth. In fact, they were misled because they thought that was p53's function, where in fact, the wild-type gene acts to protect, acts as a tumor suppressor, acts to protect the DNA or the cell from damage. So it's actually a three hundred and sixty degree difference in function, based on the fact that others were working with the mutant forms because they were isolating them from tumors or tumor cell lines which had made mutations.

Hughes: Is this sort of thing a worry in the back of scientists' minds, that maybe they are working on the wrong version of the molecule or the wrong virus? I mean, I'm thinking also of the development of the AIDS vaccine, where there was concern at one stage that the laboratory strain of HIV was not the one that was circulating in the population, particularly in Africa. All this work had been done on this particular lab strain that might not be relevant to the real world.

Pennica: Right. I think that's a worry that every scientist has, and you have to make sure you're not working with an alternative splice form. We now know that one base change can change the function of a molecule. So now we have methods where you can screen populations to look for polymorphisms or changes and different splice forms. The computer programs we have now can analyze a gene and pull out different splice forms,

so it's easier to look at the different splice variants or polymorphisms than it was twenty years ago. Now that we have these programs available.

Hughes: And would that be one of the first things that you would do in starting a new project?

Pennica: You first have to clone the molecule. If it's already cloned and known, then yes. Then you can look to see what the variants are. But you don't know the function of these variants. So a lot of the projects that we've worked on since then have shorter 3-prime ends or 5-prime ends or missing chunks in the middle, and you say, "What do these do? Why are they important? Are they important?" It takes years of work to figure out whether one that might be thirty amino acids shorter at the 5-prime end is relevant, or has anything to do with making a tumor or preventing a tumor from forming. It's critical to know that they exist, but then it takes a lot of time to figure out whether those differences are important.

Hughes: And what about actually obtaining the molecule? If it's not derived from a cell line that is already in Genentech's possession? Is that something you get from literature, to go back and see who's working on this?

Pennica: If it's been cloned, you mean?

Hughes: Yes. Or not cloned, too, if you're just beginning a project, and you need the protein.

Pennica: Well, we try to isolate it. I mean, that's the thing that—

Hughes: So you would do that here.

Pennica: Yes. We would try to find a cell line. The first thing you'd do is either try to find a cell line that makes a lot of the protein or a tissue that expresses a lot of it. So you'd grind up a heart, or a liver, or a lung where you think it might be made and try to purify it. Again, that wasn't my expertise. The protein chemists would do that. And they would get it down to a single protein. We wanted something that had an activity, so we would assay for it. With t-PA the assay was to see if the protein dissolved artificial clots in a test tube. With TNF, the protein killed cells in a petri dish, so that's a nice assay. But if you don't have an assay, if you don't have some function, then it's ten times harder. So you know that there's a molecule out there. You have to have some way of identifying it because how do you know you've ever purified it, how do you know the function? That's why I said every protein that we've worked with, or every cloning project that we've done, has been a challenge because there's always something different that you have to worry about.

Hughes: It's interesting, isn't it, that because of the way, at least the media treats it, and maybe even—and I should ask you this—in the way the paper's written up: It's the cloning and the expression that become the big things. Those are the triumphs. The sequence of events has to be there in order to get to that particular stage, but somehow, and I think it's understandable, because I suppose that's considered fairly routine and unexciting. The exciting part is the cloning and the expression, am I right there? These other stages kind of drop out of the story that's being told.

Pennica: Back then, it was the thing to clone and express a new molecule. You all of a sudden had something that killed tumor cells, for example, for TNF. That was very exciting. Nobody knew what the protein looked like. That to me is so exciting. What does the molecule look like? Does it have anything similar to other molecules? And there had been so few molecules cloned that you couldn't compare it to anything. And now it's not enough. You can't just publish a cloning paper unless it's something very bizarre that someone's been working on for a hundred years, twenty-five years, thirty years, that all of a sudden they clone. But now, the journals want mechanism. They want to know what this molecule does. They want to know what role in the body it has, and so you have to do a lot more than you had to back then. Although, back then, given the technology and the time, it was a huge amount of work. So just because things have progressed now, people clone things in a day, where it took years. It's a whole different set of criteria for what the journals will accept these days.

Hughes: And that must have meant changes in Genentech's organization, too, or at least beefing up certain parts of the organization. What I hear you saying, and correct me if I'm wrong, is it's not just enough to identify, express the molecule: You have to start on the way to showing function.

Pennica: Exactly.

Hughes: So the people who are showing function aren't the same people, necessarily, who are doing the cloning, right?

Pennica: Exactly.

Hughes: So then you would have to hire all those people who are into the biology and the functional part of it.

Pennica: Initially, I was doing the cell-killing assays, and then when we were doing hundreds and hundreds, we'd give it to another group who would do it in 96-well format, and then they would give us back the activity data. A whole other group would optimize, make sure everything was perfect, and give us the information back so that we could continue cloning. So all of those people were critical. So it was very easy to determine who went on a publication, because you could not do it without these people.

Hughes: And does it work that way today?

Pennica: It still does work like that today, especially, because we have an animal group that does all the tumor studies. We have an immunology group that makes the antibodies. We have assay groups. You cannot work alone, isolated. We tried way back in 1980; we had to be jack-of-all-trades. So I was doing a little bit of protein chemistry, a little bit of assay work. But today it's much more efficient and everything moves much faster by giving it to the experts. "Do this for us. Will you please help us with this? Do this." It's a well-oiled machine here now.

Hughes: But is the science, perhaps, for the individual less interesting, because you are doing—you're using the same approach time after time rather than being a jack-of-all-trades?

Pennica: Well, for me, I found it more stimulating in the early days, I think, because I was learning; I was doing different things, and I had to learn how to use an HPLC machine and an FPLC machine. Frustrating, but I was able to do it, but each day was something new and different, and it was a whole different environment back then, where if you needed to do something, you learned it. You had to do it yourself because there wasn't enough people here to do it, and I enjoyed that. And now you hand it off. So it doesn't feel like you have as big a piece of the pie, I guess. But you are in charge here. Again, I have charge of five projects that I'm working on, and so I'm the principal investigator, but it's different. It's a different feeling for me at least.

Hughes: I suppose it's what inevitably happens with the evolution and success of a company.

Pennica: Oh, sure. And that's a good thing. I guess it's good because we can do things faster and quicker than most people and that's why we have been successful. But for the individual scientist, it's a different world here now than it was twenty-three years ago.

Hughes: And you probably lose people as a result of it.

Pennica: Oh, sure.

Hughes: The people that don't work so well in the compartmentalized environment. Where they go, I'm not quite sure because even academia, academic science, is more that way, isn't it?

Pennica: Right. I've been so fortunate because I've worked on so many incredibly exciting projects. I can't believe how lucky I've been to work on t-PA and TNF and urokinase and a few others I haven't talked to you about yet. But that is what has kept me here for so many years, because it is always stimulating. Now we have a group that determines whether there are proteins that are up-regulated in tumors, and so then we pick what we want to work on, but those proteins have already been discovered. What we do is try to push the experiments along to see whether you can make an antibody against that protein which will kill tumors in mice. That would be a wonderful thing. But again, it's not as much discovery for me. I found it a lot more exciting in the early days because you were discovering new proteins. Today the proteins we're working on are known. The exciting part now is: Will what I'm working on become a cancer drug?

Hughes: Yes, I see.

Pennica: A different focus, I guess.

Hughes: You're further along in the process.

Pennica: We're further along, right. Molecules may need to be cloned, but again, we say to a group, "Clone this." Three days later they come back, "Here's your clone." You know, it's a whole different thing. It's not the exciting thing of getting the sequence back and saying, "Oh my God, that's what it looks like." It's a whole different thing. But I had a lot of those successes, more than most people.

Hughes: Have you had opportunities to go elsewhere and looked at them with any seriousness?

Pennica: I've never looked seriously. I've gotten many, many calls. But I always say, "I'm happy here." I think it would be hard to start over somewhere else. It would be very difficult because it has been exciting, and I can see the progress that has been made here. It would be tough for me to leave.

Hughes: Well, it's good that you're happy.

Pennica: Yes.

Hughes: Anything more on p53?

Pennica: I don't think so. I think, again, there's a lot of effort and interest, and they have an annual meeting, p53 meeting, every year.

Hughes: Do you go?

Pennica: I went once to the meeting, just because I wanted to see the progress that had been made. It was about five years ago. Quite exciting because Arnie was there, and he would introduce me, "She's the woman who cloned p53." That was exciting, too. Many people are still working on it. Whether it's going to be a drug someday, again, that's still speculation. But now they at least know that this mutated protein is found in half of all tumors.

Hughes: I gather that Genentech is not working on it anymore?

Pennica: We're not, no.

Hughes: Why was that decision made?

Pennica: Well, we were helping out Arnie, and at the time we were working on it, there didn't seem to be any clear drug at the end.

I didn't know the patent situation when we were working on this. I don't know if Arnie ever wrote a patent on this. He may not have. That I don't know. I'm certain, well not certain, but I'm pretty sure Genentech did not write a patent on this. We were just helping him out at the time. Dave said, "You want to work on this?" I said, "Sure."

Hughes: Do you ever say no?

Pennica: No, I never said no because it was always exciting, something new. I learned something from every project that I did, and it was so much fun it's hard for me to describe how much fun it was.

Hughes: After the t-PA project, when, understandably, you needed more direction from Dave presumably than you needed afterwards because you hadn't cloned, did he more or less drop out of the picture in subsequent projects when you knew how to clone?

Pennica: When I knew how to clone, he would be there for advice. He had less of a role than he had in the beginning of the t-PA project, where it was every day showing him data, and we would decide what the next strategy was. So as I learned, he had less and less

influence. I'd see him once a week or show him my data. He had a vision and an insight that was terrific.

Hughes: I'm interpreting, but from what you told me last time, I got the picture of you, at least in those early days, as working pretty intensely and independently. I mean, I think you said something about not being in the social swim, for a variety of reasons, but mainly because your nose was in the science. In contrast, I get the feeling in those very early days about the—maybe up until the time that you came—that the handful of scientists that were here were really talking to each other all the time. Consequently I'm wondering, do you think you ever missed out? I'm not thinking so much of the social aspects but just the scientific exchange that might have occurred if, as I'm picturing it, the main person you were interacting with was Dave.

Pennica: I probably did miss out because I was totally bench-focused, so to speak. I had a goal, and I was known as not socializing and going around and talking about what other people were doing, except with the people who were directly involved in the projects that I was working on: Gordon Vehar, Bill Kohr, and Dave. But I didn't go around and find out what Axel Ullrich's lab was working on or Peter Seeburg. I just didn't. I didn't have time. The lab work is so time-consuming. It doesn't lend itself to walking away because I usually had four things going at once.

Hughes: Were you an exception that way? Do you think the others were walking around to other people's labs more than you were?

Pennica: I think so. Dave probably not.

Hughes: Well, and Axel impresses me as a pretty science-driven person as well.

Pennica: Yes, he is, and he probably was, too, in the lab all the time. But again, he was on a different floor so I didn't interact with him. I knew who he was. But I didn't find out what he was working on. So I sort of had blinders on, and I continue to be like that. It's good and bad for me. [laughs]

Hughes: You get to the goal.

Pennica: Right. True. And I think it helps me get to the goal quicker than the competition because there are a lot of people—who are no longer here—who would walk around and talk to everybody, and they weren't as interested in doing the lab work. But I loved it. I just had so much fun because it usually worked. It worked for me, and it was a fun thing to do, and I miss it. But it's too hard to go back.

Hughes: Well, what about the cardiotrophins? Should we talk about them next?

Pennica: Yes. I need to break. [tape interruption]

Hughes: Diane, I think you were going to say something about uromodulin.

Pennica: So in 1987, we embarked on a project because some researchers had discovered an activity that they had isolated from the urine of pregnant women that was reported to be a potent immunosuppressant molecule. They found that it inhibited antigen-induced T-

cell proliferation and monocyte cytotoxicity in vitro, at very low concentrations, and they also had shown that it was a high-affinity ligand for interleukin-1, as well as a number of other immunosuppressive activities. The reason I wanted to talk about this is because there are some projects in science that you work on for a long, long time, and they don't turn out to be that spectacular. But you do learn something, no matter what you work on, and this is something that I always tell the people who work for me: That even though you may work on something that may never go anywhere, you learn something, and you learn how to approach the next project.

So this sounded like a very exciting project, uromodulin, and we went about cloning this protein by conventional means, once again getting protein sequence and screening the library, and found that it was a protein of 616 amino acids that turned out to be identical to the Tamm-Horsfall urinary glycoprotein, which was the most abundant protein in normal human urine. So, in fact, that is a little bit amusing, but we did learn something. Tamm-Horsfall glycoprotein had not been cloned before, but the amino acid composition was identical, and we were able to deduce the fact that what we had cloned was, in fact, this protein. We were fooled because it wasn't a pregnancy-specific protein at all. It took a lot of work and not all things pan out, but basically, sometimes, things like that happen in science. And again, I don't know what has been shown in the literature as to the function of uromodulin or Tamm-Horsfall urinary glycoprotein because I haven't followed it. We dropped it after this. That was basically the end of the project.

Hughes: And you dropped it because it was the most prevalent.

Pennica: Yes. In fact, it wasn't a challenging cloning project once we knew what it was. But when we collected urine samples from males, females, and pregnant females, we found that the protein was the same in all those samples.

Hughes: Not too diagnostic for pregnancy then.

Pennica: Not at all. [laughter]

Hughes: I think there's also humor in science.

Pennica: Yes, that's true.

Hughes: Oh, good. All right. Well, shall we stop for the day?

Pennica: I think so.

Hughes: And carry on the story next time?

Pennica: Yes.

Hughes: Yes.

Pennica: Because there's a couple stories: the CT-1 story—

Hughes: Shall I turn this off?

Pennica: Yes.

[End of session]

**INTERVIEW 3: AUGUST 6, 2003**
[Tape 4, Side A]

Hughes: We'll start today with the history of cardiotropin 1?

Pennica: Yes, and what I thought I'd do is give you a little bit of background to explain why we got excited about this project. It's still exciting because I have collaborators now who I'm dealing with all over the world—three manuscripts, in fact, on my desk right now from scientists who are still working on it. So maybe one of these people will discover something exciting.

We discovered a new molecule, which is so exciting to me. Just to begin, to tell you a little background, we were interested in cardiovascular disease because it's the number-one killer in the United States and Europe. Unfortunately, every thirty-four seconds a person dies of cardiovascular disease, and there's over a million deaths in the United States alone. Over six million patients in the US and Europe have been diagnosed with congestive heart failure, which I think is terrible. Interestingly, the one clinical finding in people who have heart disease or who are dying of chronic heart failure is that they have an enlarged heart, which was puzzling, initially. This excessive enlargement of the heart is known as cardiac hypertrophy, and this results in an increase in the size of the heart muscle cells themselves, but not an increase in the number of cells. So basically the heart is stretching.

To tell you a little bit about some of the features of congestive heart failure, you can have damage from a heart attack or valve disease. The ventricle dilates and changes shape, and this is caused by hypertrophy of the cardiac myocytes. The myocytes are the individual cells that make up the heart, and the heart doesn't pump efficiently. So what happens is that you get excess fluid that builds up in your lungs, and that's called congestive heart failure.

At the time we started working on this, the mechanisms involved in hypertrophy were relatively unknown. They didn't know what molecules cause this, why this is happening, but it usually resulted from damage to the heart muscles themselves. There's something called left-ventricular hypertrophy, and it's a powerful risk factor for coronary heart disease and congestive heart failure, and it's usually associated with being male and with advancing age, interestingly enough. The most common cause of hypertrophy is high blood pressure, so you have to watch your blood pressure. This is a fascinating picture, which shows cardiac hypertrophy caused by high blood pressure. The normal heart is about 213 grams, and a hypertrophied heart is almost twice the size, so it just stretches. This is an amazing picture that was published in 1949 to show that they knew about this way back then, but they didn't know what caused it.

There's also something called exercise-induced hypertrophy, which I thought was fascinating. You have a normal heart muscle cell, called a cardiac myocyte, and if you do isotonic exercises, like running, swimming and basketball, what happens—and this is quite interesting—is that the myocyte length increases, and there's an increase in the diastolic volume in your left ventricle. If you do isometric exercises, like weight lifting and wrestling, on the other hand, the diameter increases. And this is something called pressure overload. The pulmonary artery, or your aorta, becomes constricted, and what

happens is that your heart wall increases in thickness, so you get two different types of hypertrophy. You get stretching or you get an increase in the size.

This was all new to me when I started this project, so I thought it was fascinating. Then I looked into trying to figure out: Why is hypertrophy induced? You have adult cardiac myocytes, and these are terminally differentiated cells. They stop dividing shortly after you're born, and in response to any stress or certain stimuli, like exercising or high blood pressure, you have some heart muscle injury. Any demand for increased work by the heart, which can include exercise, the heart cells adapt to this increased pressure or workload by activating what's called a hypertrophic process. It's initially compensatory, but it can become pathological. It can go through a transition where it becomes pathological. We were interested in what factors turn on this process, going from compensatory to pathological, and are there different hypertrophy factors for the different stimuli. For example, if you exercise, is one protein made to make that length increase in the myocyte? If you have a heart attack, is there another factor that's made? We wanted to know what protein caused this.

Hughes: And is "we" you and your RAs?

Pennica: I was working with William Wood at the time, and this was a project I started shortly after Dave left. [pause]

So I didn't want to study the factors that are known. Some of the genes are induced and increased during the hypertrophic factor process, but we were interested in finding something that was new. We developed a hypertrophy assay that was quite unique, which I though was quite classy at the time. We took newborn rat hearts and isolated the heart cells from these hearts. We put them in 96-well dishes, these little plates that have ninety-six wells. You may have seen them.

Hughes: Yes.

Pennica: We waited twenty-four hours. You add the substance you think causes hypertrophy, and you stain the cells with a dye so you can see them clearly under a microscope, and you score them visually to see if they have stretched. It was a really simple assay. You can test substances to see if the cells go from looking all rounded, to stretched.

Hughes: I see.

Pennica: Which is quite amazing. And so we had an assay. Just to show you what it looks like, we scored them based on the size of the cardiac myocytes in a dish. Normal cells are all small; they look like regular cells, but we knew some compounds that would induce hypertrophy, like phenylephrine. We scored them on a score from three to seven, where seven was maximum hypertrophy, the cells were as big as they're going to get, and three was normal-sized cells.

Hughes: This is just looking under the light microscope?

Pennica: Yes. They're purple because we stained them with crystal violet. So we thought, great, we have a wonderful assay where we potentially discover unknown hypertrophy factors. Anything that might be known, we can put on these cells, and see the response.

This was a heroic effort by a woman named Kathy King, who spent hours, days, months, looking under a microscope, to look for subtle, subtle changes because it's not that dramatic. It would be great if it would go from small to big, but in some cases it went from here to here, and she was able to see a difference. If it weren't for this woman, working so diligently on this assay—that's why you need the people to do work like this—I couldn't have cloned CT-1. It was just tremendous that she did this.

So we tested a number of factors, and like I said, phenylephrine was one, and there was another compound called LIF, leukemia inhibitory factor, which will become important later on, that seemed to cause this change from no stretching to fully stretched and extended cells. So we had an assay—and that's one thing for any cloning project: You need to know what you're testing for—so we had an assay, the cells get big, that was easy to see. I mean, that mimicked what occurred in your heart. People knew that there's a cell-type called embryoid bodies that we decided to use as a source to try to find novel hypertrophy factors. Initially, these are mouse embryonic stem cells. You've heard a lot about embryonic stem cells, and we took embryonic stem cells that are normally undifferentiated. What happens if you normally plate them on a layer of other cells called fibroblasts—and you can also grow them in the presence of LIF, or leukemia inhibitory factor? What happens is: If you remove the fibroblast feeder layer, or you remove LIF, the ES cells differentiate. They divide, and they become little embryoid bodies, little round circular balls, that, interestingly, spontaneously beat. So in a dish, you can see these little things pulsing. It's amazing. They also display heart-specific markers, or proteins, that are produced, and they're a source of ventricular myocytes. You can actually isolate ventricular myocytes from these little embryoid bodies. Again, they're microscopic. You could see in a petri dish all these little specks, and you look under the microscope, this is exactly what they look like, little balls. So, we thought, great, we have an assay. We have a source of factors, unknown things that people had not yet discovered—the fact that they beat, they're mimicking what's happening in the heart. So maybe there is something that the embryoid bodies produce that can make the heart cells stretch. That was our hypothesis; this is what we were guessing. So we got lucky. This was such an exciting project for me.

We did find that hypertrophy was induced by the embryoid body-conditioned media. The conditioned media is whatever the cells are sitting in at the time. It's just like a broth or a soup. We would take media that did not contain embryoid bodies, put it on cells and stain them, and the cells looked the same, and then we took media that these little embryoid bodies had been cooking in for twenty-four to forty-eight hours, and the cells got big. So this was exciting because we thought, great, we have a source. We have a source of factors that cause hypertrophy. We didn't know what it was because there are some known substances that will do this that had been published in the literature.

Here's a beautiful picture just to show you what the stretched cells look like. You can stain for a marker called atrial naturetic peptide, which is this yellow color surrounding the nucleus, and you can see, these are called sarcomeric units. The cells stretch, look like little train tracks. But this is what happens to your heart when they're stretched like that or when you exercise. So we had an assay, we had a source, and now we decided to do an expression cloning project where we would take these embryoid bodies and the media—am I making this clear so far?

Hughes: Yes, you are.

Pennica: Great. I thought this was so much fun. We took these embryoid bodies and incubated them until the media gave a hypertrophy score of seven, which is the maximum stretching that you can get. Therefore, we knew that they were secreting a hypertrophy factor. We extracted RNA from these embryoid bodies and made a cDNA expression library, transfected pools of clones into 293 cells, which are human embryonic kidney cells, so we had pools that we put on separate dishes. Each pool contained different clones, and we incubated them for four days without serum, and then we took the media from these cells, put them onto cardiac myocytes, and we had Kathy King look at the cells and see if she saw stretching of the cells. And again, we had pools of 40,000 clones. So any activity, unless it was very robust, was going to give you a minute, minute signal.

Here was our strategy. We had ninety pools that contained anywhere from 10,000 to 15,000 individual clones, meaning individual messenger RNA, that could cause hypertrophy. So one out of 15,000 may be the clone you were interested in. We didn't get any positives, and the assay score was three. So she looked at hundreds of dishes that we transfected. Then we had tested 300 pools where we used smaller-sized pools, from 1,500 to 5,800 individual clones per pool. Again, no positives. At this point she's looked at close to 400 wells under a microscope. Actually, more than that because we repeated this many, many times. Again, the assay score was three, meaning no hypertrophy. Then we made the pools even smaller, only 400 to 1,000 clones per pool, and all of a sudden, in one of the pools that had 700 individual clones, she said, "I think I see something, and I'll give it a score of four." Now, that could be just junk; it could have been her eyes or the day or whatever, but we got one pool.

And then in another pool, where we even broke it down further, where we had seventy-five to close to 200 clones per pool, she got another positive where she scored it a four. Again, such a subtle change you almost cannot tell, but her eyes were so used to looking at this. She said, "There is something there." So we had two pools, one that contained 700 clones and one that contained 190. We broke it down even further because you want to get that one clone that has the activity. That's the goal, right? So this was so exciting. When we had a pool size of 190—we took the smaller size pool; we thought that would be easier to start with—we got a hypertrophy score of four. We broke it down to eighty clones per pool, all of a sudden it went to five; twenty, a little bit higher; and when we had one clone she gave it a score of six. We got so excited because we thought we have something here. This was the first expression cloning project I've done. And this was so exciting because we found something. Now, you get excited initially, and you say to yourself, what if it's something known?

Hughes: Yes, yes.

Pennica: That's a drag because even though it sounds like a very straightforward project, this took a long time, over a year, to get this far. We had to develop the assay; we had to develop our embryoid bodies system. There were a lot of hit and misses here. It sounds very smooth as you go through it, but we thought, great, we have something. So you have to see if it's real. And so we took this purified clone. You can see here that in the absence of media from this one clone, the cell is very rounded, but then when you put the media from this one clone on the cells—it is very stretched and beautiful. So we got very excited.

So we called this molecule cardiotrophin or cardiac myocyte hypertrophic factor. When we went to sequence the DNA from this clone to see if it was unique, in fact, it was unique, which was so exciting because it meant we found something that nobody had ever seen before in the world. Interestingly enough, it was related to—it belonged to a family which included LIF, which remember I mentioned earlier on, leukemia inhibitory factor. The family also includes ciliary neurotrophic factor, and a few other members, oncostatin M, that are very similar. But there was weak homology, so we knew we had a new member of this family, which was so exciting. So again, between the other members of the family, IL-6, interleukin-6, interleukin-11, CNTF, oncostatin M, LIF, there was a very low homology, about 20 percent homology between CT-1 and the other members of the family. It wasn't tremendous, but we knew it was good enough to make CT-1 a member of this family.

Hughes: That's structural homology, right?

Pennica: It's amino acid sequence homology.

Hughes: But can you leap to the conclusion from that that there's going to be some functional homology as well?

Pennica: Good question. We didn't know. Because we knew that nobody had ever tested these other compounds to see if they caused hypertrophy before. So that's a great question, and we had to do that. So here, we call these the LIF family of cytokines. I mentioned all of these to you. And LIF was cloned in 1984.

Hughes: Not by Genentech.

Pennica: No. Not by Genentech. CNTF also in '84, oncostatin M in '86, IL-6 in '87, IL-11 in 1990, and then, ten years later from when the first family member was cloned, we cloned CT-1 in 1994. And they're all roughly the same size, anywhere from about twenty to twenty-five kilodaltons in size. These proteins are known as cytokines, secreted proteins that seemed to act on other cells. That's the definition of a cytokine. A lot had been studied about the other family members: LIF, CNTF, et cetera. They knew that CTNF was involved in neuronal cell survival. They knew that these other family members were involved in bone metabolism, blood vessels, hematopoietic cells. They seemed to have multiple functions, and macrophage differentiation, ES cell differentiation. So knowing the activity of the other family members, we thought to ask what CT-1 does, to see if CT-1 has similar activities.

This is a picture of a structure of the family, showing different cytokines here in the circles, and then the receptors that they bind to on the cell's surface in order to exert their activity.

Hughes: This is the cell membrane?

Pennica: This is the cell membrane, yes. And interestingly, each one of these family members uses a common receptor subunit called gp130, and that is critical for its activity. So, to answer your question, do other members of the LIF family induce cardiac hypertrophy? Nobody had ever tested this before, so that was the first logical question, great question. And when we did this, we found, in fact, that the other family members do induce

hypertrophy. CT-1 seemed to be the most robust although LIF was very potent as well. Oncostatin M was potent, the other family members not as much. So that was something new that we included in the paper that we published. As I mentioned, because it has homology, we tested whether CT-1 functioned in other assays where LIF has activity. But I don't want to go into that because all this data is included in the paper. But just to tell you the background, we did find similar activities. Because CT-1 had so many different activities, we didn't think it could be used as a drug that you could just inject or make an antibody that could be injected, to decrease the size of the enlarged heart cells, because it had so many other activities in your body. You want to make sure a drug just does one thing, otherwise you could hurt the patient.

But one collaborator—I now have collaborators all over the world who are still working on CT-1—he is in Marseille, France, and he found that CT-1 supported the long-term survival of spinal cord motor neurons. If you can find a factor that can support the survival of a motor neuron, it could be a therapeutic agent for things like ALS or spinal muscular atrophies. So this was very exciting, the fact that we found CT-1 caused these neurons to survive longer in culture than other factors that have been looked at before. We published a paper in the journal *Neuron*, which was quite exciting, and we got the cover photograph showing a motor neuron here in red, that CT-1 has been added to—it's quite dramatic. I thought this was a beautiful picture. [*Neuron*, Vol. 17, Issue 1]

Hughes: Yes, isn't it though?

Pennica: It looks very different from a heart cell.

Hughes: Absolutely.

Pennica: CT-1 causes this activity. You can see the neuron starts out like this and then extends branches out, and that's what CT-1 does. So we thought that this could be a physiological motor neuron survival factor. Other investigators I'm collaborating with now are investigating neuronal properties. We made a knockout mouse where you delete the CT-1 gene and try to figure out what happens to the mouse. We have another collaborator in Germany who has made a triple knockout, where you knock out three genes at once. He's knocked out CT-1, LIF and CNTF, three of the family members, and he's analyzing the mice right now, and I got a draft of a manuscript just a week ago from them. So this is quite exciting for us.

At this point, we don't know the true function of CT-1. It's still being investigated. From 1994, we're still working on this, and we know things that it does, but in the body it may work in collaboration with other cytokines; it may work in collaboration with other family members. We still don't know.

Hughes: When you collaborate with these different groups, is your function usually more or less the same? Are you, for example, usually the cloners or is there a technology that is usually yours, and then you rely on other people for aspects of the research?

Pennica: It depends. For a project like CT-1, where we already have the clone, we would have people writing to us, saying, "I saw your exciting paper and I want to do 'x' or 'y'—can we have your clone? Can we have antibodies? Can we have protein?" And my thought is, give them to everybody who requests them because I'm not able to do everything. At

some point I move on to another project because Genentech may have determined that this is not worth pursuing at this time. It is interesting, but may not be a potential therapeutic target. I use my expertise in that I tell the collaborators if there's other assays that they need done, we will do it for them because we have a hypertrophy assay here. We will give them protein—we've made protein for them. We can make more antibody. We just let them do their thing, and I get papers in the mail saying, "We're putting you as an author on these papers."

Hughes: Does the legal department enter into this process?

Pennica: Oh, sure. Yes. I can't send out anything unless the legal department approves, and we have the patent on CT-1, which is great. So any discovery, I guess—I'm not exactly sure how it's structured, but we send them a Material Transfer Agreement form where we tell them that we would like them to tell us their results, and if there's anything that's patentable to come out, we have to review their papers before they can publish them.

Hughes: And is one of your arguments—this is put very simplistically—to the legal department: This is an avenue of research that we probably will not be pursuing and, so, let them do it and give us some of the credit.

Pennica: Yes, let them do it because one of these researchers is going to find something really exciting. It just takes years. It may be something we never thought of.

Hughes: Is part of the Material Transfer Agreement that your name or a Genentech scientist's names will be on the paper?

Pennica: Not necessarily. It's up to the researchers. They decide whether your contribution was enough to warrant authorship, and in some cases I am not put on the papers. In other cases, they feel they couldn't have done the work without the things I supplied them with: proteins, antibodies or the clones, so I think in that case it's warranted. I help them out as much as I can. I review the papers. We have a very good review system where any papers that come from the outside—or even inside papers—go through an internal review where we have two people scrutinize the paper and give a very critical review before it gets sent out to the journal. This is very helpful because they can pick out things that you may not have thought of, and hopefully will strengthen the paper, so it's always a good thing.

Hughes: Is that review both scientific and legal?

Pennica: Yes. It is both scientific and legal because legal looks at it thinking—is there an invention here? Is there something new that we haven't thought of? And if there is, then we write a patent.

Hughes: Right. Yes.

Pennica: And in most cases our patent usually covers what they have, what they are doing. In many cases it's basic research because these are universities I'm collaborating with, and they're all over the world. That's fun and exciting. Many of these collaborators I've never met.

Hughes: How do you feel, Diane, when a project that you have been working on and really scientifically engaged in, turns out not to have at least immediate therapeutic promise, and therefore you have to drop it and move on?

Pennica: It's disappointing because you've put so much time and effort into it. But every project you do, you learn something, and I'd never done an expression cloning project before. I knew nothing about cardiac hypertrophy, so learning all about the process and what was involved was exciting. So you move on. You move on to the next one and say, "Oh, what can I learn next?" That's what is so exciting, and the fact that people are still interested in this almost nine years after the protein was cloned is great. I think people are still interested enough to study this protein. I dropped it, long ago, but they may find something that may be a potential drug at some point. You can't get too disappointed. You can't have every one be a t-PA. [laughter]

Hughes: Exactly. Was it your decision to drop the project?

Pennica: It was a consensus, because everyone thought this protein had too many different activities. Since all the other family members have multiple activities, we tested CT-1 in all of those assays as well, and found CT-1 does this, it does this, it does this, et cetera, and we thought if we inject it into people it might have too many side effects.

[Tape 4, Side B]

Hughes: —seminar of the morning is on WISP. And what does that stand for?

Pennica: Wnt-induced secreted protein.

Hughes: Wind?

Pennica: W-n-t. So I'm going to tell you a little bit of the history and the background of how it was started in my lab. We finished the CT-1 paper in 1994, and I did a number of things between then. But I'll go to the most exciting one next. And this project began in 1997 as a collaboration with Arnie Levine, and if you remember, Arnie Levine was the collaborator who I did the p53 project with, way back.

Hughes: Yes.

Pennica: Arnie was on sabbatical at Genentech at the time, and we were between directors, so he spent the summer here. He would review projects that we were working on. I came into his office one day. He said, "I have a great project for you." I had shown him some of the things I was doing to look for targets in stomach cancer, and he said, "I have a great, exciting project for you." And that's all I needed to hear. Arnie was always so bubbly and excited about research that he could make anybody excited about a new project. He said that we should look for colon tumor antigens that may be therapeutic targets using the Wnt-1 signaling pathway as a cancer model.

Just to tell you a little bit about colon cancer to begin with, there are two key colon cancer mutations. Eighty-five percent of colon tumors contain mutations in a gene called the APC tumor-suppressor gene, which stands for adenomatous polyposis coli. That's why people call it APC. Forty-eight percent of colon tumors that lack APC

mutations contain mutations in an oncogene called beta-catenin. So our rationale, just to give you a little bit of background about the pathway for using the Wnt-signaling pathway as a cancer model, is that: Many, many years ago, Harold Varmus's lab determined that Wnt-1 was an oncogene, meaning a tumor-causing gene, and if you ectopically express it in mice, they develop mammary tumors. So the Wnt pathway mimics what occurs in the majority of human colon tumors as a result of an APC or beta-catenin mutation.

In a tumor cell, that either has a mutation in APC, has a mutation in beta-catenin, or if you have Wnt-signaling, beta-catenin levels go up, the half-life goes to four hours. Normally, beta-catenin levels sit around in the cell, and it gets degraded very rapidly and has a half-life of about thirty minutes. But when you have a mutation in a tumor cell, the beta-catenin molecule does not get degraded. What happens is that beta-catenin protein increases in the cell, it gets shoved into the nucleus by some mechanism, and it binds to transcription factors and turns on genes that are thought to play a role in growth control and tumor progression. So these two mutations cause the same thing. You can either have a mutation in APC, a mutation in beta-catenin, or Wnt-signaling. The end result is the same: Beta-catenin levels go up, it gets shoved into the nucleus, genes are turned on, and you get a tumor.

Why? What genes are turned on? So just to tell you a little bit about what Wnt does in a cell, we needed an assay, just like we did for the CT-1 project. We needed a cell line that potentially made a protein that would induce this tumor—could be hundreds of proteins. But we were looking for something that would cause this change. So we took a mouse mammary epithelial cell line called a C57MG cell, and we put the Wnt gene in these cells. When you did that, the cells changed shape, and they became elongated, similar to what happened in the CT-1 project, and they lost contact inhibition. Normal cells in a dish, once they touch another, would stop growing. So the loss of contact inhibition meant that the cells would pile up on one another, and they became elongated. By eye, it was a quite dramatic change from a normal cell to an elongated cell once you put Wnt in the cells. When the cells are not transformed, we can also look at the beta-catenin levels. In the normal cell, beta-catenin levels are very low, I mentioned, to begin with. Once you have Wnt in these cells, you get a tremendous amount of beta-catenin being over-expressed.

So we had a cell line, then, that we could use to find proteins, again just like the CT-1 project, because these cells mimicked a tumor cell. And we thought, we can look for proteins that were unique. [tape interruption]

Suppressive subtractive hybridization, basically the key word there is subtraction. We had the parent cell line that did not express Wnt, and we had a cell line that we had over-expressed Wnt in, and we did a subtraction. So we looked for all the genes—we did it basically in an array. Not to get too technical, we did an array of what genes are different. You subtract out everything that's the same. You look at all the genes that are different, and we got hundreds of genes that are different. When you do this cloning, you end up getting a library of clones that are just partial pieces of genes. We ended up sequencing inserts from 2,000 clones, many of which were known genes, many of which were unknown genes. What I ended up doing over a period of many, many months, because it took months to sequence these 2,000 clones, was to look for proteins that might be unique and that might be related to other genes. I saw in one of these little

snips of DNA—it was only seventy base pairs long—but when we got the amino acid sequence for that stretch, there were, I think, three or four cysteines that appeared to line up with the cysteines in a family called the CCN family of growth factors. And so we had, once again, isolated a brand-new member based on seeing the sequence from that one small fragment of DNA. We had hundreds of others. There's other things that we can still look at, but it turned out to be a brand-new member of this family, which was quite exciting. Because it was novel, we could name it something new. So again, another exciting project.

The CCN family of growth factors contained three members, connective tissue growth factor, CYR61 and Nov, and we isolated three unknown proteins, which we named WISP-1, WISP-2 and WISP-3 because they were related. They were cysteine-rich secreted proteins; cysteine-rich meaning they contained thirty-eight cysteine residues, which made it very difficult to purify these proteins. It still is difficult. The exciting thing about this family, since we knew nothing about WISP-1, is that when we looked in the literature, very, very little was known. There were only about thirty papers published. Now there are hundreds of papers that have been written on this family since we started this project. We were looking for something involved in tumor formation. I knew nothing about any of these family members. Again, that's why it was exciting. We found out that these members were involved in cell proliferation. That's important in cancer. They were involved in attachment and migration, which is important in metastasis. They were involved in wound healing, differentiation, and angiogenesis, meaning the infiltration of a tumor by blood vessels, and some of them in fact were implicated in tumorogenesis. And so we got very excited, because we thought WISP-1, WISP-2 and WISP-3 could also play a role in tumor genesis. So, we may have found three new proteins involved in tumor formation.

So we did a literature search, and we found out what all three of these family members did that could be involved in tumor formation. We found that CYR61 was up-regulated in pancreatic cancer and breast tumors. Connective tissue growth factor was found to be elevated in melanomas and sarcomas. Other people had looked at the protein called Nov and found it in a very rare childhood tumor called Wilms tumors. They found elevated levels of this protein. A lot of these family members have been implicated in cancer. We thought, great, we have three brand-new members that might be implicated in cancer. We just had to find out their function. We decided to focus on WISP-1 first.

We characterized WISP-1, we sequenced it, we looked at its structure and found it had a fairly high homology to the other family members, between 35 and 45 percent homology. So it was higher homology than the CT-1 project I talked about earlier. WISP-1 had thirty-eight cysteines. It's a bigger protein; it's forty kilodaltons. Since our focus was colon cancer, we decided to look in human colon cancer cell lines to look to see whether the protein is elevated. When we did that, we found that in fact in a number of cell lines, WISP-1 was elevated. We also looked at the DNA copy number and that we do to determine whether the gene is amplified. When a gene is amplified, this can cause problems in the cell as well. So we took a number of primary human colon tumors and found that, in fact, in the majority of them, the DNA copy number was about two-fold in 60 percent of the primary human colon tumors that we looked at. It wasn't very dramatic, but it was at least two-fold. People sometimes don't get excited about two-fold, but I remind them that if your temperature is elevated two-fold, you die.

Hughes: Yes. Good analogy.

Pennica: Another thing that you have to do in any project is determine—once you find out that this might be a target for cancer, you have to find out where else in your body it's made. And if it's made everywhere in normal tissue, that's not a good thing because it means that it probably has a role and a function there, so if you try to inhibit its activity you could mess up something critical.

It was expressed in a number of normal human tissues, but it was significantly over-expressed, or elevated, in human colon tumors. About 84 percent of human colon tumors we looked at had elevated levels of WISP-1. So you can imagine a localized target. We did not find it in the normal colon, but we found it very highly expressed in colon tumors. As you can see, these little spots are the expression in a colon tumor versus a normal colon, where there's no expression here. So that was quite exciting. We did a number of other assays to determine what it does.

We are now in the process—I won't go through any of the other details of the science because that can be found in the publication—but we're now in the process of writing a paper to see whether WISP-1 might be involved in metastasis. It may play a role there so we're quite excited. Another lab at Genentech has taken over that project, and they are working on that right now as we speak. We don't know what kind of target WISP-1 might be, but it's still quite exciting because it's still high-profile at Genentech.

Hughes: And your lab still has a role?

Pennica: I act as an advisor, and we do assays for them. If they need things done, we help them out, or we give them reagents and cell lines. I got this group excited about this protein and they are taking it over because I have five things I'm working on now.

Hughes: And that's all right with you?

Pennica: It is.

Hughes: You don't feel proprietary?

Pennica: No, because they'll include me on the publications so it's great. It's better that I learn something new and move on.

So anyway, this was quite an exciting paper, and it still could play a critical role in tumor formation. But that was our goal, just to find a downstream target in the Wnt pathway that might play a role in tumor formation. We might have found something. The fact that we found something unique is quite exciting. I've been very lucky to discover so many unknown proteins that had never been cloned before. That was fun for me.

Hughes: Well, does that satisfy you in terms of what we have said so far, what you have said so far, to cover at least the highlights of the science that you've been involved with?

Pennica: Yes.

Hughes: Maybe you could make a comment about the technology and how that has impacted both the efficiency and also the direction of the research that you've done at Genentech over, was it twenty-three years?

Pennica: Twenty-three years. Yes, the technology has changed dramatically. Back in 1980, we had to do everything ourselves. For every project we worked on, if you needed something done, you did it alone. We did work in teams; you couldn't do anything in isolation. As I mentioned, Bill Kohr did all the protein sequencing because he had the expertise to do that, but the cloning was so labor-intensive at the time. Now it is cookbook. There are kits that you can use to do everything. The kits have become more sophisticated, so in the WISP project I did use a kit, but it was still a little bit labor-intensive but unbelievably easier than what we had done twenty years before.

Hughes: Give me an example of something specific that had changed.

Pennica: So you could make a cDNA library in a week in 1997, whereas back in 1980, it may take months to make a cDNA library that you could analyze. Just the steps to make the cDNA was time-consuming because we had to make all of the components. When you have a kit, you just take out a little tube and you add it to the reaction. It was very different twenty years ago. We had to make our own gels. That's another good example. I was making my own gels, which often took an entire day, to make all the reagents, to pour the gel, to have it set, to let it sit overnight, to use it. Now there are whole companies dedicated to making gels. It's in a Ziploc bag, you tear it open, pop it in the machine and load your sample. It takes thirty seconds. Unbelievable.

So things have changed dramatically, and now we have whole groups that clone what we want. They have perfected the technique, and they can, in a few days, get you a clone that you need. Everything is more streamlined. It's certainly a lot quicker, but I think the questions are a little different that we are asking now. We're now trying to determine the biology of these molecules to see if they're involved in tumor formation. Back then, we were just identifying, not <u>just</u>, but we were identifying new molecules that could be involved in heart disease and cancer. You have to learn all about the biology of the molecule, also, to see if it's relevant or does anything of interest. Clearly, it does.

Hughes: Obviously, you're describing a tremendous revolution in efficiency and just general ease, but at the same time you are in a sense losing control in the fact that you have to depend on a kit, or you have to depend on a sequencing group or—

Pennica: Yes, absolutely.

Hughes: Did this require sort of a shift in your thinking about how you did research?

Pennica: Yes. When you rely on other people, you rely on their quality, their efficiency and their—we are fortunate at Genentech to have super-team people, who do incredible work here. But if there's one kink or one person who just doesn't do their job efficiently, then it can waste a lot of time. For example, Kathy King, who was a superstar on the CT-1 project, without her expertise and painstaking patience to look under the microscope at that hypertrophy assay, the project never would have gotten done. So there are superstars, and then I have worked with other people who are not as

efficient, and it's very frustrating. When you do it yourself, you spend the time and effort to do it right, but you have to rely on a lot of other people sometimes. They may not work as quickly or efficiently as you do, but we're pretty lucky here. We have a good team. It has changed, though; it certainly has changed.

Hughes: Do you have any feelings in general about the fragmentation of research?

Pennica: I think it makes us do things a lot quicker. I know it does. I liked having a project all to myself like I did in the old days. Now I feel there are a lot of cooks, which is a good thing and a bad thing. It's hard to explain. You are at the center of a project in the old days, and now you're more of a team player.

Hughes: Yes, yes, I see. Which I think for you, because I pick up—and tell me if you think I'm there—that at least in those early days, you were a perfectionist. You had your way of doing things and you weren't going to be interrupted by Tom Kiley or anybody else. [laughter]

Pennica: Right. Right.

Hughes: So I'm thinking that it probably did take quite a shift.

Pennica: It did.

Hughes: For you, as a person, to all of a sudden being reliant on somebody whose efficiency—well, whose perfectionism might not have been at quite the level that yours was.

Pennica: Right. It has helped me, and it also hurts me in a way because you get frustrated when people don't have the same level of fanaticism as you do.

Hughes: Yes. Yes.

Pennica: I always think I am fanatic, but I think that's what has helped me be successful, the fanaticism and attention to detail. Many people don't put that much time into doing something and many times their experiments don't work. Well, my experiments worked 90 percent of the time because I was fanatic about them. It took me a lot longer to do things than other people, but a lot of people left science because they didn't want to be that fanatic. It takes a lot of patience, and you have to go through a lot of failures. But I would do something thirty times until it worked. It may not work because you're adding the wrong buffer, or you have too little or too much buffer, and you don't know what it's supposed to be. Back in the old days. I would do an experiment forty times until it worked. That's the way that I was taught when I was doing my undergraduate work, and in graduate school, to try a hundred things until you do get it to work. So I didn't like to give up.

Hughes: Do you try to pass on that approach to your laboratory people?

Pennica: I do, yes. I try to tell them when you're running a gel and you only have two samples, throw in a few more samples because you never know, you might find something exciting. Of course, it's easier to just run two samples, but if you have a chance to look at five other DNA, RNA or protein mixtures that may be related, put them on the same

gel. It takes more time, it takes more effort, but that was my approach: Instead of doing less, do more.

Hughes: And is that a characteristic, or an openness to that approach, that you look for when you're taking people on into your lab?

Pennica: Well, it's hard to measure. You never know how much enthusiasm someone is going to have. I try to find somebody with a spark always and who is ready to jump out of their chair to do the research, so they usually want to do more than less.

Hughes: Good. Well, I have a few more general questions if you feel happy with what we said so far.

Pennica: Sure.

Hughes: Do you have until twelve?

Pennica: Yes.

Hughes: As I see it, you've lived through three regimes at Genentech, the Swanson, the [G. Kirk] Raab and the [Arthur] Levinson. I know from what you've told me before that your nose has been in the science, and I have the strong impression that you weren't as interested in the larger picture at Genentech.

Pennica: Precisely.

Hughes: Nonetheless, it must have had some impact, and I'm wondering if you could say something about any shifts in general functioning of the company as a whole that you might have noticed as a scientist as you moved from one CEO to another.

Pennica: Well, I've been very fortunate in that I've been given great projects. I've worked on tremendous projects, and Bob Swanson was always so excited about everything we were working on. He wanted this company to succeed, and he made it happen. I interacted a lot with Bob Swanson because we were such a small company at the time; there were only sixty people. I interacted rarely with Kirk Raab because we were getting much bigger at the time. I don't know how many people we had then, but he certainly knew who I was. But he never came around to talk to me, so I didn't know him that well. And Art Levinson, I have interacted with since I got here. He got here four days after I did, and so I interacted with him as a scientist, so he knew me well. There's never been a time when I wasn't excited about the science.

The management changes have been excellent, as far as I'm concerned. Because I didn't interact with Raab, I can't comment on how the company went at the time. I think Art's doing an excellent job, and Bob Swanson also did a tremendous job. So clearly we've become successful, as evidenced by our stock going up, and all the drugs we're making that are now helping to save lives. So I feel fortunate that I was a part of that in the beginning, and it's continuing now. Hopefully, I can make more contributions, but one is more than most people ever ask for or more than most scientists ask for.

Hughes: Well, in 1990, as you know, Roche acquired a controlling interest in your company.

Pennica: Yes.

Hughes: Did that make any difference?

Pennica: Not to me.

Hughes: Not to you.

Pennica: Not to me at all. I have been fortunate that the higher-ups usually leave me alone and let me do the science. I don't get involved in the politics. I don't usually know half of what's going on as far as the politics go here. But that's a good thing because I stay focused on my research and that's my strength. The Roche takeover, when they acquired part of us, I never noticed a thing. Nobody ever came in my lab and said, "You have to switch working on what you're working on."

And when Arnie came, I was working on gastric tumors, and he suggested that I work on colon cancer, and so I started working on the Wnt project. So for the longest time, I was working on what I was excited about. Dave Goeddel had always said that, "You can't make people work on something unless they're excited about it. Because if you tell them what to do, they will not do a good job." So I've always had exciting projects, and I just delve in and learn everything I can about it, and try to do the best I can. That's a good strategy. If somebody says, "Oh, I have no interest in working on this or that," then they're never going to do a good job. So it's a good strategy. I've never said no; I've always enjoyed everything I've worked on and learned a ton, a tremendous amount.

Hughes: Do you have any philosophy about when, if ever, a scientist, or I guess in this case, you, should address the ethical dimensions of the science that you or Genentech is engaged in?

Pennica: I'm not sure what you mean.

Hughes: Well, I guess it was most apparent in the beginning, even by the time you came in 1980, it was beginning to die down. But you know, there was the recombinant DNA controversy. Should scientists tinker with the genetic endowment of human beings? It was quite a debate in the nation as a whole and also eventually internationally with Asilomar and that whole history of events that went on.

Pennica: But I don't think people understood—

[Tape 5, Side A]

Pennica: —cloning human beings, again, that's been in the news these days. What we're doing is we're trying to identify genes in your body that are important for a particular function, for example: What causes cardiac hypertrophy? What causes colon cancer? These are simple questions, and there's probably not simple answers. We clone one gene, and we hope it may be the magic bullet, but it might not be, at least not in isolation. You may have to use a combination of things. But when we say cloning, we mean trying to find the piece of DNA in your body that is responsible for a particular function. And so you isolate that gene, put it into a cell, and make a protein, and then can you use that protein,

like t-PA for example, to dissolve a blood clot. In fact, in the case of t-PA, a simple protein was enough to dissolve blood clots. We tried to do the same thing for CT-1. In this case, find a gene that causes your heart cells to get bigger, or undergo hypertrophy. Well, you wouldn't want to inject CT-1, because it would make the heart bigger, which is not a good thing. So, what we would want is an antibody against it, to shrink the enlarged heart cells.

If people understood that you're not putting anything foreign into your body, you're putting in proteins that your body already makes, sometimes in short supply. For people who have blood clots, clearly they don't have enough t-PA circulating in the body to dissolve them, for whatever reason; it could be genetic. So you're trying to supplement the lack of enough t-PA. Human growth hormone, or HGH, is the perfect example, for children who have a growth deficiency. We wanted to isolate that gene and make growth hormone so we could treat children who lack sufficient HGH in their bodies. So to me, if people think of it that way, it's certainly a great thing. Perhaps enough people hadn't explained it in these terms. I don't know. I just think there were too many people against it who didn't understand its potential. I think it's the most tremendous thing that's ever happened for disease treatment.

Hughes: There are always lines over which at least some parts of society think that you should not go. I'll give you an example with the growth hormone. I think most people would agree that using growth hormone for children that are severely inhibited in terms of the growth pattern has got to be a good thing. But apparently, there was an effort at one stage to convince the parents of a population of short children, but not dwarf children, that to show whatever image a parent or this society—I'm not quite sure where these images come from—of the height that a child should reach, and you turn to growth hormone for what would be, in essence, a more aesthetic use than a therapeutic use. It's a very gray line where you go from one to another. That's one example of that comes to mind where things might go too far.

Pennica: Oh, there's certainly going to be some unethical doctors who prescribe it for the wrong reasons. We hope there's not many of those people. But clearly, that's not our intent.

Hughes: Yes. And it's not something that you worry about.

Pennica: Well, it's disturbing when you hear stories like this, but you hope that they're few and far between. We're not going to hear many stories like that.

Hughes: In terms of Genentech's legacy—that sounds very elegant and overwhelming. Genentech was, of course, the first to base itself on recombinant DNA, a pioneer in the field, and I'm wondering what the upsides and the downsides are of being the first and the foremost in a new area.

Pennica: I think there's only an upside. It's just like publishing a paper: You always want to be the first. That was my strategy and so you worked ten times harder than everybody else to be first because I didn't want to be beat on the cloning projects that I was working on. But you never knew who was working on them. So being first as a company, I think, is only a good thing. You set a standard, for sure, because the image could get tarnished, but hopefully it has not so far. I think people continue to say that Genentech is the star

of the whole biotech business, and I think it's just a good thing. I feel very fortunate to be here for twenty-three years.

Hughes: You said something off tape about how people react when you tell them that you're a scientist, and I'm wondering if you'll say more about that, and also is that how you define yourself?

Pennica: Well, I've had many people just say, "No way, you can't be a scientist." I don't fit the profile. I say, "What is a scientist supposed to look like?" But when they ask me what I do, I do say, "Scientist. I do cancer research." That's easy for most people to understand. So I'm very proud of the fact that I do research.

Hughes: And do you define yourself to yourself as a scientist? Is that what you are?

Pennica: Yes. I think so. I think it's a good description: You're trying to discover new things, and in this case we're working on a lot of genes now that are known, but we're trying to see whether these genes are involved in tumor formation. So that is also a discovery process. It takes a long time just to work on one gene, to find out whether it plays a role, or an important role, in tumor formation or tumor maintenance. That's what I'm working on now. I have five proteins that we're trying to figure out what role, if any, they play in prostate cancer and ovarian cancer. So I say, "Yes, I am a scientist." Because if I'd say molecular biologist or cloner, people don't understand that. I think scientist is easier.

Hughes: Well, at last count, and I'm sure it's changing, you had thirty-seven patents on which you were inventor. I've counted them up.

Pennica: You did. [laughter]

Hughes: Well, I'm sure there may be more pending. And say something about how you value those patents in reference to your publications.

Pennica: Well, the patents are something necessary for Genentech. I think it's very prestigious if you are an inventor on a patent application because it shows that you were involved in the thought process of defining something new and novel and finding a new use for something, or finding a new use for something that was already known. It's an honor to be on a patent application. But those don't get published as readily. They get published, certainly, but for the scientific world you're more known for your publications than your patents.

Hughes: And so if you had to choose between them?

Pennica: Oh, the publications.

Hughes: I thought you were going to say that.

Pennica: Yes, absolutely.

Hughes: There's the scientist. [laughter]

Pennica: Yes.

Hughes: Comment on your role in various litigations. Are there stories to tell?

Pennica: One in particular was quite amusing. I don't know if I told you this or not; maybe I did. I can't remember. But there was a litigation—it was a patent hearing in Germany, and they were questioning the validity of our t-PA patent, saying we didn't make an invention. They claimed it was obvious anybody could have done it. And so I went with Steve Raines and a few other Genentech legal people. It was an arbitration where there were three patent examiners deciding the verdict. I can't remember—it was Kabi, I can't remember. No, it was not Kabi; it was Behringer Ingelheim.

Hughes: Oh, yes.

Pennica: I think so. So there was a group of lawyers on one side. It was an L-shaped table, and the patent examiners were in the middle. The Behringer lawyers were facing us, and there were three or four Genentech people presenting the case. I was the only woman in the room. The patent examiners were asking questions, and we would answer. I didn't speak at that point. The lawyers would answer the questions from the patent examiners. I would whisper things into our attorney's ear just to make certain points that we never knew if this would work, for example. It's not obvious that you would ever get the clone. It's not obvious that you would ever find something. They were asking questions to us as well as the other side. We were never introduced to the other side to begin with. I don't know how this happened, but I decided during one of the breaks to introduce myself to the head lawyer for Behringer as we walked outside. I said, "I want to introduce myself. I'm Diane Pennica." The lawyer said to me, and I'll never forget his words, "You're Diane Pennica? I thought you were much, much older!" He said, "I thought you were one of the administrative assistants for the attorneys." So that was quite amusing to me. It was clear that the patent examiners were favoring Genentech, and in fact we won that arbitration. The German lawyers got so upset that they weren't getting their points across that they decided to switch to speaking German instead of English, so we all had to put on headphones to listen to a translator translate the questions and answers. It was so bizarre. They decided not to speak English anymore; they decided to speak German. So that was an interesting event in my past.

We also went to a trial in London, where it was quite fascinating because all of the lawyers, including the judge, wore these wigs, these long white wigs.

Hughes: Yes, I've seen them.

Pennica: And the judge was at a table that was forty feet above everybody else, and it was just like you see in the old movies: these long robes and the wigs. I wasn't cross-examined for very long. I think I was only on the stand for twenty or thirty minutes, but they really kept Dave Goeddel up there for a long time, so he was on the hot seat.

Hughes: And again, was it the novelty of the invention that was at question?

Pennica: Yes. Yes, it was the novelty of the invention. We had Paul Berg as an expert witness on our side. They had James Watson, the Nobel Prize winner who discovered DNA, as an expert witness on their side. We had George Stark as an expert witness for us as well.

Hughes: What was Watson's argument?

Pennica: He was at Cold Spring Harbor at the time. I believe his claim was that because people at Cold Spring Harbor were doing the same thing, it was obvious to do and that it would eventually work. Well, it's never obvious that any cloning project is ever going to work. So that was an interesting trial. It was fun to see the way the trial progressed.

Then there was another trial in Washington, and I was on the stand for a while. We won that case. They asked me what the important points were. Our lawyers wanted to know how to end, and I suggested telling the jury the story about me meeting the first heart attack patient, because it tells them the human aspect of the whole trial and that we're trying to save lives. At that time we weren't a big company just trying to make millions of dollars. We were trying to save lives. And that seemed to be very effective for the jury. It was scary being up there.

Hughes: Did legal counsel prepare you before you went up on the stand?

Pennica: They did. And I made suggestions on things that I thought would be useful to put in, or include. They seemed to like me as a witness. The lawyers liked me because they said they needed sincere people who the jury could identify with. I don't think the other side was too hard on me in Washington. They were harder on Goeddel. Maybe because they saw me shaking.

Hughes: I think one has to acknowledge that probably gender and age and all those things are factors. It's not just a matter of the legalities and the science.

Pennica: Absolutely. I think that makes a huge difference. I was lucky, by meeting Desiré Collen because that first meeting where I wasn't kicked out because they thought I was one of the guys' daughters.

Hughes: Yes, I know it. Amazing.

Pennica: That was an advantage.

Hughes: Well, time is flowing, so I will ask you one more question and that is: If you had to pick one contribution of which you are most proud, what would it be?

Pennica: Oh, of course, t-PA. Absolutely. I probably worked as hard on all of the other projects that I've worked on—because I've been so fanatic about every one of them—but certainly t-PA's given me the most satisfaction. Meeting heart attack patients and getting letters and cards and phone calls from people has just been so rewarding. I mentioned before that there will never be another t-PA. It would be nice if there were others. I feel very fortunate and very lucky to have been involved in something like that and had a great group of people to work with, who helped: Bill Kohr, Dave Goeddel, Gordon Vehar. They were all instrumental in the project, and Desiré Collen as well. But I definitely worked hardest on that project, for sure, and it would be hard to work that intensely again.

Hughes: Yes. Well, is there any more you want to add?

Pennica: I don't think so at this point, other than maybe looking at my old t-PA notes and seeing if there's something I missed or forgot to tell you.

Hughes: That sounds good. Well, I thank you.

[End of interview]

Transcribers: John Lynch, Christine Sinnott
Final Typist: Lea Barker

APPENDICES

APPENDIX A

## DIANE PENNICA

EDUCATION:

1973 B.S. - State University of New York, College at Fredonia

1977 Ph.D. - University of Rhode Island

## RESEARCH AND PROFESSIONAL EXPERIENCE

| | |
|---|---|
| 1971 - 1973 | Undergraduate Fellowship in the Department of Biology, State University of New York, College at Fredonia |
| 1973 - 1976 | Teaching Assistantship in the Department of Microbiology, University of Rhode Island |
| 1976 - 1977 | Instructorship in the Department of Microbiology, University of Rhode Island |
| 1978 - 1980 | Postdoctoral Fellow, Roche Institute of Molecular Biology, Nutley, New Jersey |
| 1980 - 1988 | Research Scientist, Molecular Biology Department, Genentech, Inc. South San Francisco, California |
| 1988 - present | Senior Research Scientist, Molecular Oncology Department, Genentech, Inc. South San Francisco, California |

## SOCIETIES

American Association for the Advancement of Science

International Cytokine Society

American Association for Cancer Research

## AWARDS AND HONORS

| | |
|---|---|
| 1984-85 | **Chosen by Science Digest** as One of the Scientists Involved in the **Top 100 Innovations of the Year** for Work on Human Tissue Plasminogen Activator |
| September 27, 1986 | **Distinguished Alumni Award**, State University of New York, College at Fredonia |
| December 27, 1987 | **Chosen by New York Times** as One of Four People for the Article "The People Behind Some of the Bright Ideas of 1987" |

| | |
|---|---|
| April 23, 1988 | **Service to Humanity Award**, Fredonia Chamber of Commerce, Fredonia, New York |
| May 14, 1988 - | **Commencement Speech** to College Graduates at State University of New York, College at Fredonia |
| April 13, 1989 - | **Inventor of the Year Award**, Intellectual Property Owners Foundation |
| 1990 | **Genentech President's Award** for Outstanding Achievement |
| June 30, 1991 | Nominated for Induction into **The National Inventors Hall of Fame** |
| November 1995 | **Named to the SUNY Alumni Honor Role** for excellence in career achievements (State University of New York) |
| September 30, 1996 | Nominated for the **Lemelson-MIT Prize for Inventors** |
| May, 1997 | Chosen to be **included in a chapter in the book "Prescriptions for Profits: How the Pharmaceutical Industry Bankrolled the Unholy Marriage Between Science and Business"** by Linda Marsa |
| January 21, 1998 | Chosen by **PhRMA** to represent Genentech in television and print ads on the impact and potential of t-PA for stroke patients |
| January 29, 1998 | **Chosen to speak to Vice president Al Gore** when he visited Genentech to announce two cancer-related proposals: an additional $4.7 billion--a 65% increase--over five years in funding for cancer research at the National Institutes of Health; and the expansion of Medicare benefits for cancer patients. |
| December, 1998 | Chosen to be **included in the book "Patently Female"** under Medical Innovations by Ethlie Ann Vare (General Publishing) |
| May 19, 1999 | Invited Speaker at the Master of Liberal Studies in Technology Lecture Series "**21st Century Inventing**" Eastern Michigan University |
| January 29, 2000 | One of three women profiled in a speech to the American Chemical Society by author, Autumn Stanley on "**Women Inventors Who Make a Difference**" |
| June, 2001 | Chosen to Give an **Oral History on the t-PA project for the Bancroft Library** at the University of California at Berkeley for The Program in the History of the Biological Sciences & Biotechnology |
| August 10, 2001 | Invited Speaker for **Career Symposium at Vanderbilt University** to Graduate Students and Post-Doctoral Fellows about Research in the Biotechnology Industry |
| July 15, 2002 | Chosen as **One of 31 Scientists Profiled on the Genentech Web Site** out of 546 People in Research. See: http://www.gene.com/gene/research/sci-profiles/ |

## PUBLICATIONS


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United States Senate
COMMITTEE ON LABOR AND
HUMAN RESOURCES
WASHINGTON, DC 20510-6300

April 13, 1989

Dr. Diane Pennica
Genentech, Incorporated
460 Point San Bueno Boulevard
South San Francisco, California 94080

Dear Dr. Pennica:

I have just learned that you are to receive the "Inventor of the Year" award from Intellectual Property Owners Foundation for dramatically facilitating the treatment of heart attack and stroke victims.

The isolation and cloning of tissue plasminogen activator is a remarkable scientific achievement, indeed, for which you should be justly proud. I am sure the availability of TPA will, in and of itself, offer new hope to victims of heart attacks and strokes. Equally important, however, is the basic knowledge gained through the insight, diligence, and expertise of individuals such as yourself. You are to be commended for your role in this pioneering enterprise.

Once again, congratulations and best wishes.

With warm regards,

Ever sincerely,

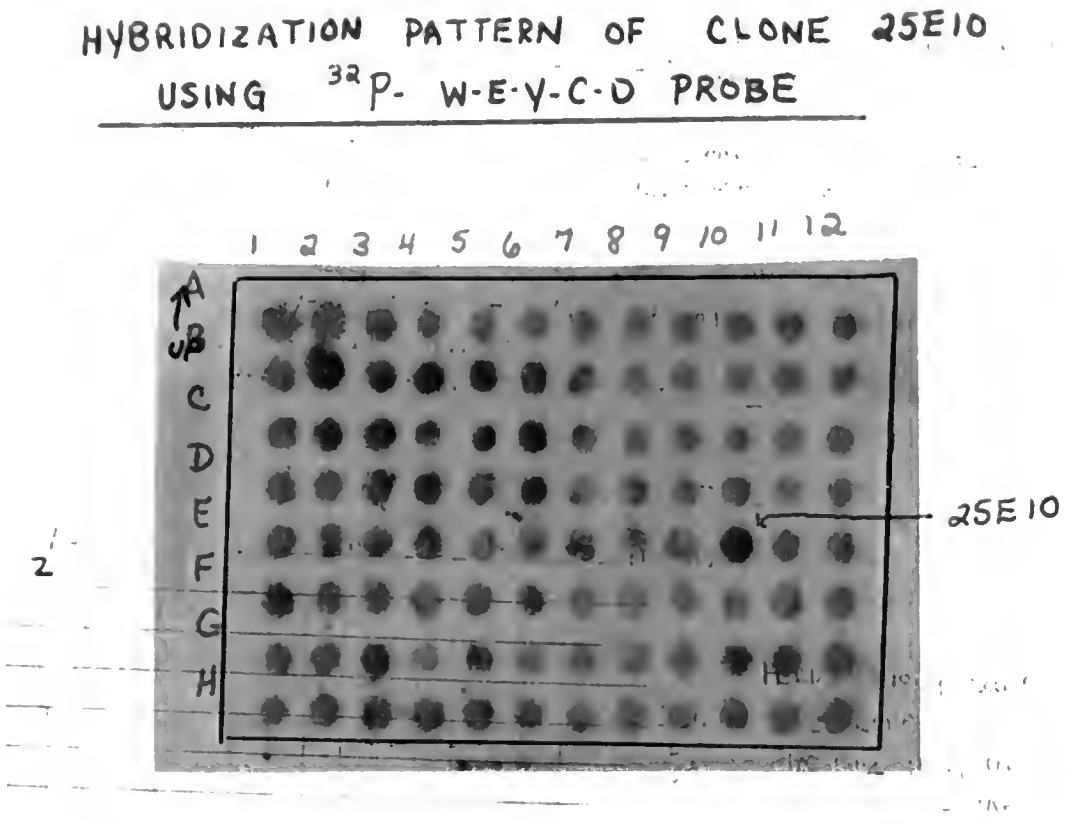
Claiborne Pell
Chairman
Subcommittee on Education,
Arts and Humanities

David V. Goeddel, Diane Pennica, William J. Kohr, Gordon A. Kehar,
recipients of Inventor of the Year Award, 1989

*Photo courtesy of Diane Pennica*

APPENDIX C

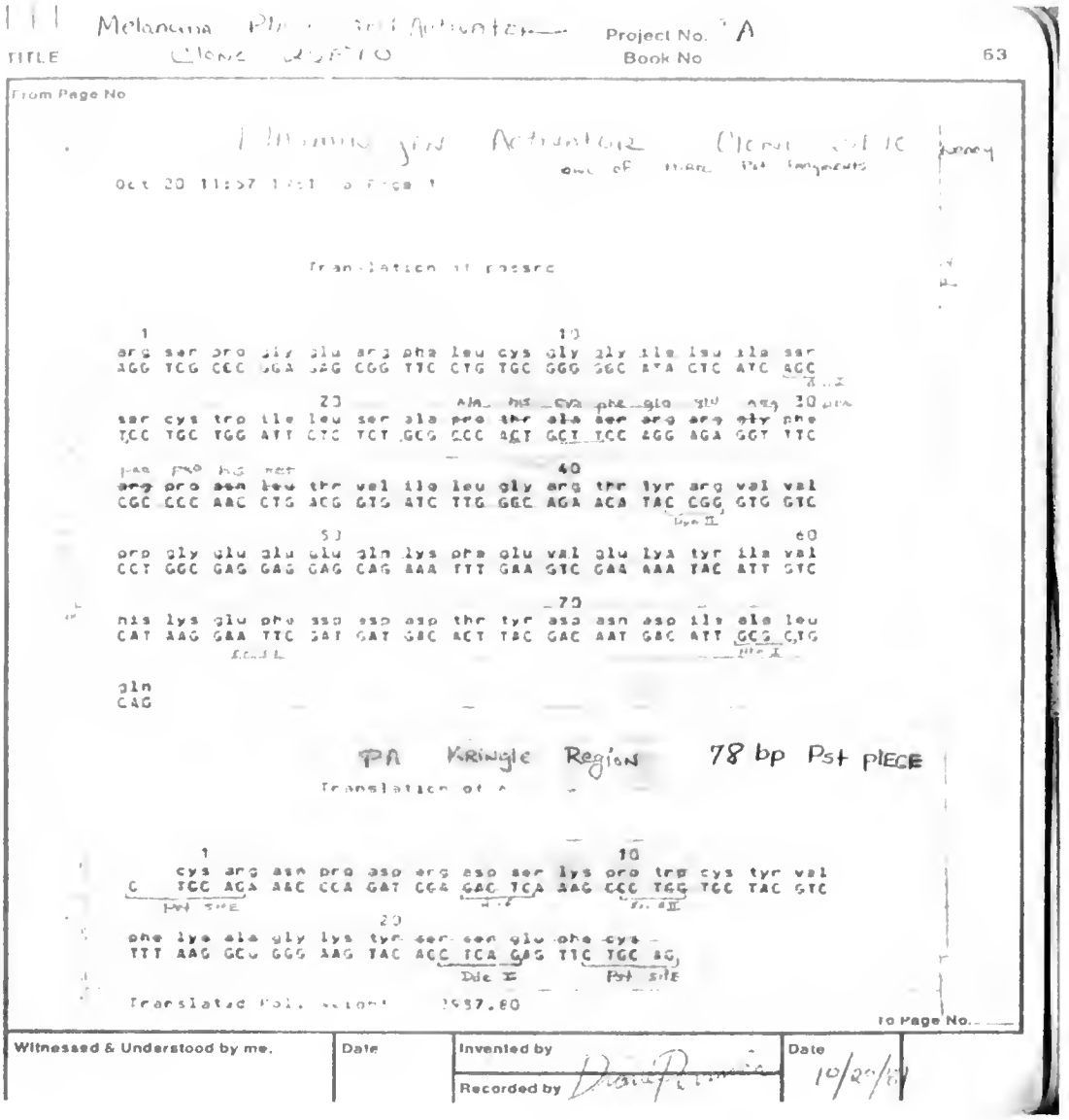
*Photos courtesy of Diane Pennica*




Photograph of the film on notebook page dated September 7, 1981, showing the Colony Hybridization of 96 of the 5,000 clones that we screened with the 32P-TC(A/G)CA(A/G)TA(C/T)TCCCA(WEYCD) probe.

Clone 25E10 was one of the many clones we chose to sequence based on a slightly darker signal with the probe than other clones.

*– DP*



TITLE Clone 25E10 Project No. A Book No 63

From Page No

Oct 20 11:57 1981 Page 1

Translation of reverse

```
  1                                                  10
arg ser pro gly glu arg phe leu cys gly gly ile leu ile ser
AGG TCG CCC GGA GAG CGG TTC CTG TGC GGG GGC ATA CTC ATC AGC
                                                    Xho I
                  20                  Asn  his  cys phe glu  glu  arg 30 pUC
ser cys trp ile leu ser ala pro thr ala ser arg arg gly phe
TCC TGC TGG ATT CTC TCT GCG CCC ACT GCT TCC AGG AGA GGT TTC
pAO  pAO  hG  met                  40
arg pro asn leu thr val ile leu gly arg thr tyr arg val val
CGC CCC AAC CTG ACG GTG ATC TTG GGC AGA ACA TAC CGG GTG GTC
                                                Dde II
                  50                                    60
pro gly glu glu glu gln lys pro glu val glu lys tyr ile val
CCT GGC GAG GAG GAG CAG AAA TTT GAA GTC GAA AAA TAC ATT GTC
                                  70
his lys glu phe asp asp asp thr tyr asp asn asp ile ala leu
CAT AAG GAA TTC GAT GAT GAC ACT TAC GAC AAT GAC ATT GCG CTG
                                                  Hha I
gln
CAG
```

PA Kringle Region 78 bp Pst piece

Translation of A

```
    1                                                  10
    cys arg asn pro asp arg asp ser lys pro trp cys tyr val
C   TGC AGA AAC CCA GAT CGA GAC TCA AAG CCC TGG TGC TAC GTC
  Pst site                  Xho I                Dde II
                  20
phe lys ala gly lys tyr ser ser glu phe cys
TTT AAG GCG GGG AAG TAC AGC TCA GAG TTC TGC AG
                          Dde I          Pst site
```

Translated Pol. sequence 1997.80

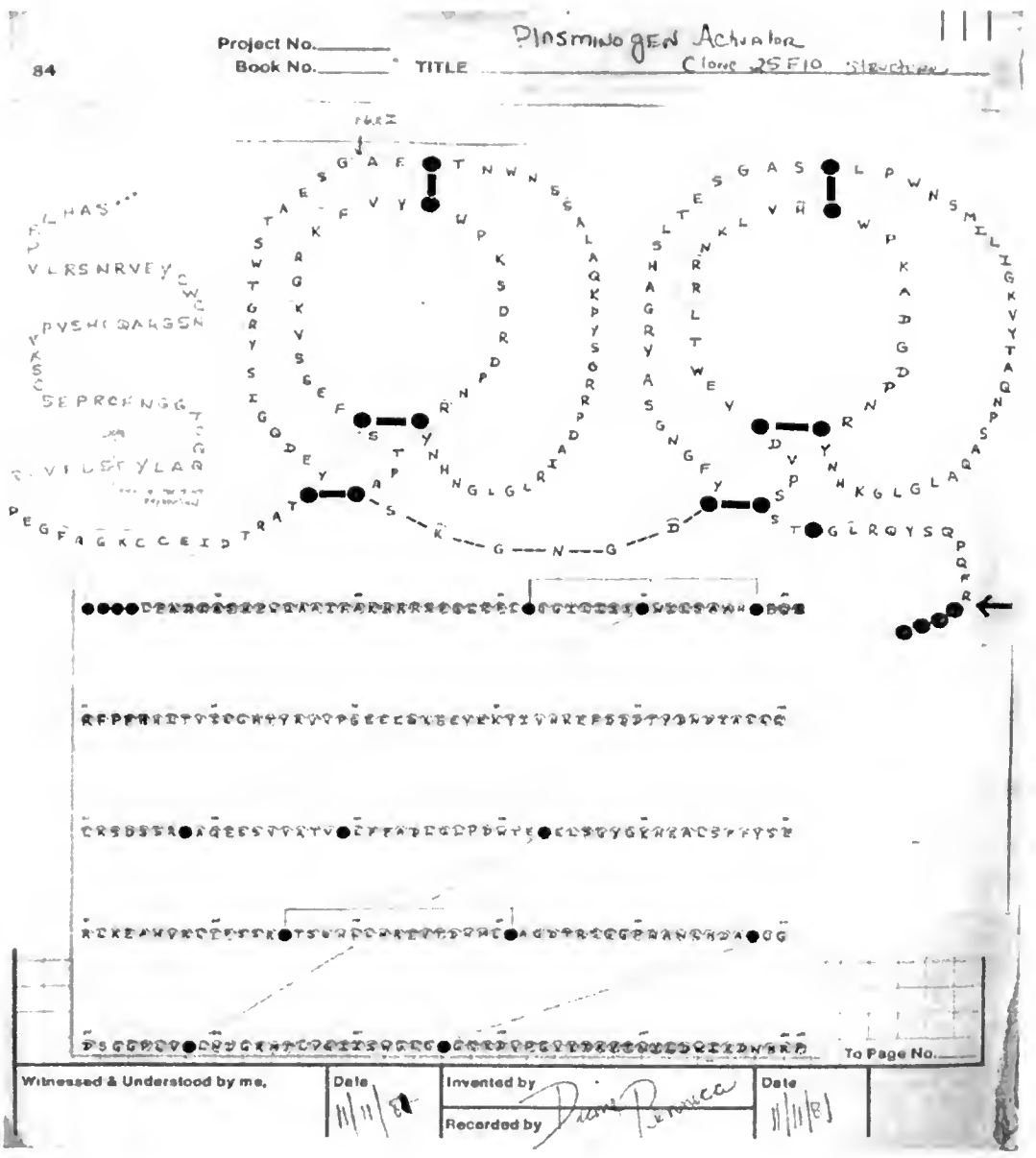
To Page No.

| Witnessed & Understood by me. | Date | Invented by | Date |
|---|---|---|---|
| | | Recorded by Dave Penica | 10/20/81 |

One of the most exciting moments in the t-PA cloning project happened on October 20, 1981, when we determined that clone 25E10 contained a portion of the t-PA cDNA. This notebook page shows the first bit of sequence from clone 25E10 that told us we had at last isolated a t-PA cDNA clone. Only one other clone out of the 5000, Clone 25B2, contained a partial t-PA cDNA sequence and it was on the same filter, but we did not choose to sequence it initially because it did not stand out from the clones surrounding it.

The thrill of this was that 36 years after t-PA was discovered as a fibronolytic agent in blood, we determined its structure by cloning.

*– DP*



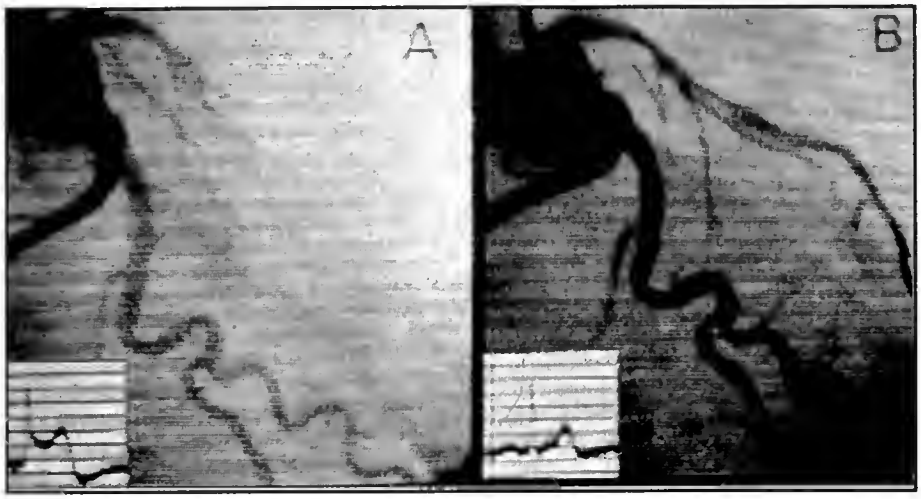

Entry from my notebook dated 11/11/81 showing the entire t-PA cDNA sequence from Clone 25E10. Unfortunately, this clone was missing a small number of amino acids from the 5 prime end of the protein. It took us another five months of non-stop work—7 days a week and 14–16-hour days—to get the remainder of the t-PA cDNA clone.

*– DP*

APPENDIX D

*Powerpoint slides courtesy of Diane Pennica*

Recombinant t-PA Restores Blood Flow in Blocked Artery




Before t-PA After t-PA

Human Patient Angiogram in the Clinical Trial

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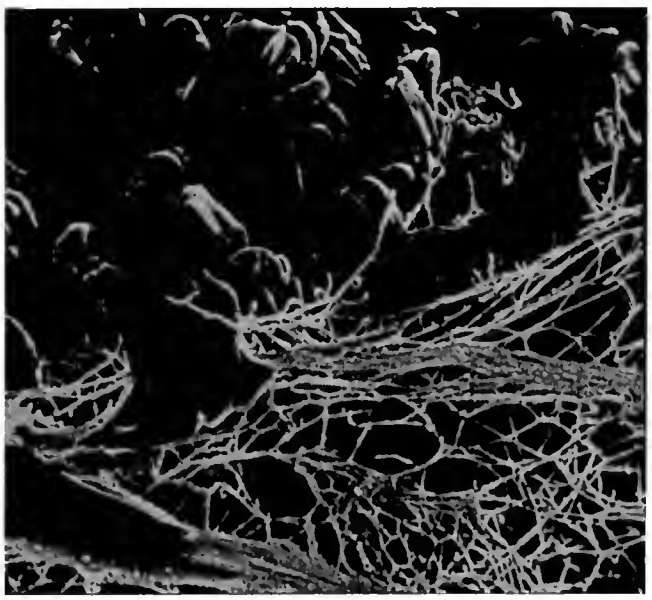
Fibrin in a Blood Clot Being Dissolved by t-PA



# APPENDIX E

*Powerpoint slides courtesy of Diane Pennica*

November 13, 1987

40 Years After t-PA was First Identified It was Approved As a Drug For Heart Attack Patients


**From:** Michael May
**Date:** October 7, 2004 7 05 06 AM PDT
**Subject: Please Forward to Ms. Diane Pennica, Chief Scientist**

***Catching Up From 1987***

Dear Ms Pennica

I was pleased to see/hear that you are still with Genentech And, like so many others I'm sure, pleased that God made you available to me on that dreadful day of December 17th, 1987

My wife had just had a post-op pulmonary embolism that stopped her heart They had already pronounced her dead when the ER physician at Plano General Hospital gave her a new drug known as TPA We were both 33 years old and our girls were 13 and 9

Today, we are both 50 and happily married after 31 years and the girls are 30 and 26 both married and college educated

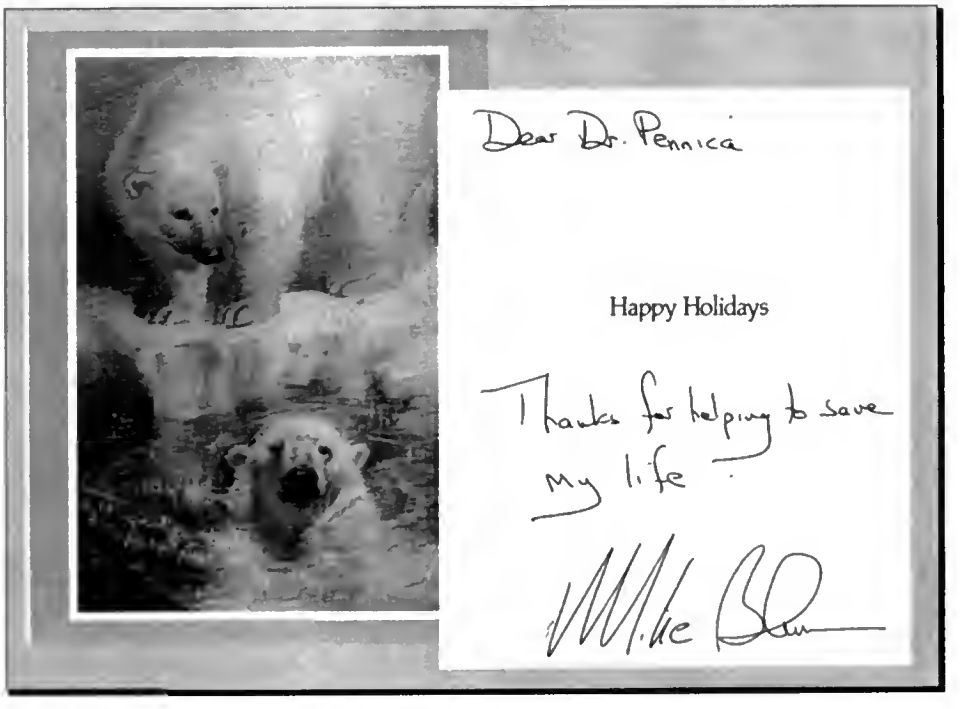
Thank you so much for your work in helping others through science

Kind Regards,

Michael J May

Steve Birnbaum: First Heart Attack Patient Treated with t-PA

Christmas Card From Heart Attack Victim Mike Blum



# Francis Wagner — Stroke Survivor

## Email from the Daughter of a Stroke Patient

My father had a massive stroke a few years ago. He was completely paralyzed on one side, didn't know who he was…

They got him to the hospital very quickly, and an astute ER doctor identified him as a candidate for t-PA therapy.

**10 minutes** after the t-PA went in, he was waving, smiling and speaking fine.

He is now home, strolling around the neighborhood and showing *No* obvious symptoms at all.

The doctors told my mother and brothers that they had never seen such an amazing recovery…

So, needless to say, my family has a newfound appreciation for the impact (and the future potential) of biotechnology.

INDEX–Diane Pennica

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.