Program in the History of the Biological Sciences and Biotechnology

Scientist and Patent Agent at Genentech

Dennis G. Kleid, Ph.D.

With an Introduction by
Coe A. Bloomberg

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

Introductory Materials

Legal Information

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

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

> Dennis G. Kleid, Ph.D., "Scientist and Patent Agent at Genentech," an oral history conducted in 2001 and 2002 by Sally Smith Hughes for the Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2002.

Biotechnology Series History

Sally Smith Hughes, Ph.D.

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

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

When Charles Faulhaber arrived in 1995 as Bancroft's director, he agreed on the need to establish a Bancroft program to capture and preserve the collective memory and papers of university and corporate scientists and the pioneers who created the biotechnology industry. Documenting and preserving the history of a science and industry which influences virtually every field of the life sciences, generates constant public interest and controversy, and raises serious questions of public policy 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 of one million dollars to support documentation of the biotechnology industry.

Thanks to these generous gifts, Bancroft has been building an integrated collection of research materials--primarily 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 advise 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. The UCSF Library, with its strong holdings in the biomedical sciences, is a collaborator on the archival portion of the Program. David Farrell, Bancroft's curator of the History of Science and Technology, serves as liaison.

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 1,600 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 (MELVYL, RLIN, and OCLC); 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. The three criticisms leveled at oral history also apply in many cases to other types of documentary sources.Yet these acknowledged weaknesses of oral history, particularly its subjectivity, are also its strength. Often individual perspectives provide information unobtainable through more traditional sources. Oral history in skillful hands provides the context in which events occur--the social, political, economic, and institutional forces which shape the course of events. It also places a personal face on history which not only enlivens past events but also helps to explain how individuals affect historical developments.

An advantage of a series of oral histories on a given topic, in this case molecular biology and biotechnology, is that the information each contains is cumulative and interactive. Through individual accounts, a series can present the complexities and interconnections of the larger picture. Thus the whole (the series) is greater than the sum of its parts (the individual oral histories), and should be considered as a totality.

Emerging Themes

Although the oral history program is still in its infancy, 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 industry. 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 has 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

August 2002

Oral Histories on Biotechnology

Program in the History of the Biological Sciences and Biotechnology

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

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

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

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

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

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

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

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

"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,"* 1998

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

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

Oral histories in process:

Brook Byers

Stanley Cohen

Chiron Corporation

Roberto Crea

David Goeddel

Herbert Heyneker

Irving Johnson

Arthur Levinson

G. Kirk Raab

William J. Rutter, vol. II

Richard Scheller

Axel Ullrich

Keith R. Yamamoto

Introduction by Coe A. Bloomberg

Dennis Kleid has proven to be a unique resource at Genentech. He combines a knowledge of Genentech's scientific contributions, from the very beginnings of Genentech, with an understanding of the litigation process. Dennis received a Ph.D. in organic chemistry from the University of Pittsburgh in 1972. Following post-doctorate fellowships at MIT and Harvard, he worked as a bio-organic chemist at Stanford Research Institute from 1975-1978. Later in 1978, he became Employee Number Five at Genentech as a molecular biologist. Because employees one to four are no longer at Genentech, Dennis's tenure is longer than that of any other Genentech employee. Dennis worked as a scientist at Genentech until 1986 when he joined Genentech's Legal Department. He is admitted to practice before the U.S. Patent and Trademark Office as a Patent Agent, and his current title at Genentech, Senior Patent Agent and Senior Scientist, reflects the fact that he has one foot in the field of law, and the other in the field of science.

Because of Dennis's familiarity with the various scientific projects at Genentech, he is ideally suited to assist litigation counsel in determining what documentation should be reviewed, and what Genentech scientists should be interviewed, in connection with patent litigation. He is a very patient teacher of lawyers with respect to complicated scientific issues such as the recombinant DNA production of pharmaceutical products. He has been involved in virtually every major patent dispute in which Genentech has been involved in the last 15 years. And over that time, he has developed a keen grasp of the legal issues that are often determinative of patent litigation and patent interferences. On a more personal note, Dennis has a wonderful, if somewhat irreverent, sense of humor, and is an absolute pleasure to work with.

Coe A. Bloomberg

Partner--Jones, Day, Reavis & Pogue
November 20, 2002

Interview History--Dennis G. Kleid

Dennis Kleid as one of the first three scientists hired on site at Genentech is an obvious choice for interviews on the company's history. Unlike most others in this series, he has remained at Genentech and hence was an apt observer of corporate science and culture as the company grew and prospered over time. In 1986 Kleid made a substantial career shift to Genentech's legal department where he continues to serve as patent agent. He can thus speak from personal experience of both the scientific and legal aspects of Genentech.

The detailed narrative which Kleid recounts in the following pages is directly informed by his two complementary positions. One "voice" is that of the scientist deeply knowledgeable in chemistry and molecular biology. A second "voice" is that of the legal expert whose scientific background and participation in specific research projects is instrumental in preparing and sustaining Genentech's legal team in the seemingly endless litigation typical of the biotechnology industry. The reader will find that Kleid's direct experience of much of the early research that transpired at Genentech is refreshed, extended, and inevitably molded by his ongoing review of the scientific and intellectual property background to patent interferences and other litigation. "My job," he remarked off tape, "is doing history in reverse."

The Oral History Process

Six interviews were recorded in Kleid's office in Building 25 at Genentech. He was a ready and enthusiastic subject. He provided a detailed outline of interview topics which guided the recorded sessions as well as documents to supplement the discussion. Kleid's preoccupation with the factual basis of Genentech's achievements and setbacks carried over into the transcript review process. He added new textual material in a few cases and a flotilla of footnotes, evidence of the scientist-cum-legal expert's attention to full documentation. We are grateful for the considerable work this represents. His expressed wish is to provide the reader with references to back up his narrative. As always with the oral histories supported by Genentech, the transcripts were submitted for review by its legal department. No changes were requested.

One might expect the man behind this labor-intensive effort to be sober and humorless. One could not be further from the mark. Although intently serious about his scientific and legal responsibilities, Dennis Kleid laughs easily, exudes a "laid-back" California style, and appears quite happy to share his views. Getting him to talk in the interviews was not a glimmer of a problem.

Sally Smith Hughes, Ph.D.

Historian of Science
November 2002

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

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I Family Background and Education

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

Family History and Undergraduate Education

Hughes

Please give me a thumbnail sketch of your family of origin, going back a reasonable distance.

Kleid

On my mother's side going back a reasonable distance would be before the Revolutionary War. The Huguenots emigrated to the States in the 1600s and her family dates all the way back to that time. Leonard Dozier came from France in 1686, Jeromie Cothonneau came from France in 1688. (Unless attributed to SSH, the interviewer, all footnotes are by Dr. Kleid.) Her family's ancestors came to California after the Civil War from Georgetown, South Carolina. Anthony White Dozier 1801-1870 and Mary Catherine Cuttino Dozier 1811-1873 and family including William Gaillard Dozier 1833-1908, Peter Cuttino Dozier 1835-1877, Leonard Franklin Dozier 1835-1917, Virginia Ellen Dozier 1838-1925, Anthony White Dozier 1842-1874, Edward Charles Dozier* 1843-1919, Melvile Dozier 1846-1936, Alvin Dozier 1848-1921, Barton Dozier 1851-1931 and Linwood Dozier 1855-1886. (*My mother's great-grandfather) Her great-great-grandfather's family had ten kids and all five of the sons who fought as part of the Confederate South survived the Civil War. At the end, when they all came back home, they decided that they would emigrate to California. Two of the sons Leonard and Melvile. went across the Isthmus of Panama and took a boat up to San Francisco, The Oregonian entered the Golden Gate March 12, 1868. taking with them a letter of introduction to a Dr. H. H. Toland, a former resident of Columbia, South Carolina, then a

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leading physician in San Francisco. He founded Toland Hospital and the School of Medicine. He bequeathed these institutions to the University of California which are now known as U.C. Medical Center. Toland Hall is right there on Parnassus Avenue, and as a coincidence, it's right next to the building that Herb Boyer's lab was in when I first met Herb Boyer in the mid-seventies. Dr. Boyer founded Genentech in 1976. I also went to University of Pittsburgh and that's where Herb Boyer went. I also met some of his postdocs at different meetings. So I had quite a number of coincidental path-crossings with Herb Boyer in the mid-seventies.

On my father's side they're Jews that emigrated at the turn of the century to New York City. Jacob Kleid (my dad's father), entered the U.S. via Ellis Island with his sister and parents prior to 1900. The family immigrated from the Galicia region, at that time part of the Austrian Empire. My father (Albert H. Kleid), came out to California during World War II. My mother picked him up when he was hitchhiking. That's how she (Alna M. Kleid), met my father. They got married just after World War II ended, and soon after that, that's when I was born, July 1946. I'm part of the oldest Baby Boomers, I guess.

Hughes

Where were you brought up?

Kleid

I was born and raised in Napa, California. When I graduated from high school, I went to Napa Junior College for a couple of years, and then I went to the University of California at Berkeley [1965-1968]. I somehow graduated from Berkeley in organic chemistry. It was very difficult for me, and I just barely made it through Berkeley. One of my classes was in molecular biology and my professor was Gunther Stent. He gave a wonderful course and I fell in love with molecular biology at that time. Gunther S. Stent, *Molecular Biology of Bacterial Viruses*, San Francisco, London, W. H. Freeman and Company, 1963. [SSH]

When I graduated from Berkeley I really just wanted to get a job, but in the early seventies there weren't a lot of jobs for kids out of college. It was an economic time rather like today's recession. Just in case, I sent away for applications for graduate school. I got six applications, and I ended up filling out the three easiest ones. The University of Pittsburgh accepted me with a teaching assistantship. So this guy from California ended up in Pittsburgh, Pennsylvania at the University of Pittsburgh--like I said, the same place where Herb Boyer also was a student at one time.

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Family of Origin

Hughes

Let's pick up some of these strands. What did your mother and father do for a living and how many brothers and sisters did you have?

Kleid

I had two brothers and a sister. My father worked at the University of California Lawrence Radiation Lab as a machinist's specialist. He helped build the atom smashers. He did metal working.

Hughes

Did he know the Lawrences?

Kleid

He didn't know the Lawrences, but he worked with Donald Glaser a lot.

Hughes

Of the bubble chamber.

Kleid

The bubble chamber, yes! My father worked on the bubble chamber. I think the last project he did before he retired was the target for the Stanford linear accelerator. So he would come home with stories of the projects he was working on and he is still today very proud of being part of the Lawrence laboratories back then.

Hughes

Did his profession have anything to do with your choice of science?

Kleid

He certainly instilled an interest in science, although he didn't finish high school until he came to California and did high school at night school. And then he took college courses at night school. He talked a lot about what they were learning about breaking the atoms apart and making new atoms. I was definitely very interested in that. From a very young age, third or fourth grade, I was going to be a scientist. It was really the only thing that I ever really wanted to do.

Hughes

Was education a priority in the family?

Kleid

It was, yes. My folks really wanted us to do well in school, and they were very happy that we were going to college.

Hughes

Where do you fall in the family ranking?

Kleid

I was the oldest son and then I had two younger brothers, but we were all very, very close in age. My one brother Don was just a year younger and my brother Ken was three years younger, but our birthdays were all within a couple weeks of each other; we're all Leos. So we used to fight all the time and pummel each other.

Hughes

Did any of them end up in science?

Kleid

No. My brother Don went to UC Davis and became a math teacher. He still teaches math at Folsom High School. My brother Ken didn't go to college. He went to Mare Island, to a school that provided technical training. I think he studied sonars. He said, "I did that for mom." After two years, he started driving around the United States and ended up in Hawaii. He was

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friends with some people from Napa who invented the windsurfer, and he used to give windsurfer lessons in Kailua, which is on the windward side of Oahu opposite Honolulu. Then he did more of that windsurfer renting and teaching on Kauai and Maui.

Hughes

Say a word or two about your mother.

Kleid

My mother also went to school when I was younger and took classes and finished high school. She became a bookkeeper for Kaiser Steel. She worked at the Kaiser plant in Napa from when I was in high school until she retired, about ten, fifteen years ago. My father also worked at Kaiser in the 1950's before he got the job at Berkeley. Napa to Berkeley, that was a very long commute. That was very hard on him.

Undergraduate Education, 1964-1968

Choosing a Major and Napa Junior College

Hughes

You said that organic chemistry was a struggle, or words to that effect.

Kleid

College was a struggle. [laughter]

Hughes

Why did you choose organic chemistry?

Kleid

I actually chose it in high school. I took biology and that was interesting, and then I took chemistry, and I liked that way better. Then I took physics and I said, "No, I like chemistry better."

Hughes

Why?

Kleid

Something about the molecules and how they interact with each other was interesting to me, and you could understand it without a lot of math. Biology was too heavily based on phenomenology, and I couldn't really understand what was going on. But with atoms, you could really imagine how they hooked together. It just seemed interesting to me. So I kept with chemistry.

I went to Napa Junior College because I had a very hard time with writing and reading. I'm slightly dyslexic, and I have a hard time writing. One of the requirements for chemistry was that you had to learn German. I was extremely poor in that, so I decided with some encouragement from my mom to go to Napa J.C. and take basic courses, and then when I went to Berkeley I could focus on the science part. That worked out pretty well.

UC Berkeley, 1965-1968

Kleid

I got through Napa J.C. okay, but then when I switched to Berkeley the classes were just <u>incredibly</u> difficult. In my first term I got two C's and a C minus, so I was on probation. Next time I got all C's. If you got below a C average for three quarters in a row they kicked you out. So the third quarter I got two C's and a B, which canceled out the C minus. But one of the C's was in physics, and it turned out that I flunked the physics final--I got absolutely zero on it. The teaching assistant was very, very nice. He convinced the professor to give me a C in the class because of what I did on a day-to-day basis in class, or else I would have been gone from Berkeley. The senior year was better. I was there for seven straight quarters and somehow made it out of Berkeley.

Hughes

Did you have any particular contact with the faculty?

Kleid

Not really. Berkeley's impersonal for undergrads. My professors were down on a stage in the bottom of a giant auditorium. I didn't get to know any professors at all.

Graduate Student, University of Pittsburgh, 1968-1972

Marriage

Hughes

Then the University of Pittsburgh. What laboratory did you end up in?

Kleid

When I went there I didn't know whose lab I was going to be in. I had a very hard time adjusting to the University of Pittsburgh because it was just so different than California.

Hughes

You had never been out of California?

Kleid

My folks had driven to Washington DC and NYC in 1964 with my grandparents in two cars and a trailer, but that was it. Prior to that, I crossed the border to Oregon once and went to the Nevada side of Lake Tahoe of few times. But Pittsburgh was really different. In the early seventies it had all these steel companies within the city limits. So it was a smoky place and smelled sulfury and buildings were all drippy looking. I had a very hard time finding a place to live, but finally I found a place and started adjusting to life there.

I had a girlfriend from Berkeley, and I had proposed to her. But we didn't end up getting married so we corresponded with each other. Then she decided that she was going to come to Pittsburgh, and we were going to get married in Pittsburgh. She told her folks that and they said, "No, no, let's bring him back." So within three or four months of arriving in Pittsburgh I came back to California, got married, and took her [Phyllis L. Innerfield Kleid] back to Pittsburgh. We lived in an old house on Nicholson Street--which is this old cobblestone street--on the third floor in this house chopped up into three rental units. We stayed there for four years--slanty ceilings and everything.

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In Pittsburgh I had again the issue of not being able to read and write very well, and here I was in graduate school. I didn't do very well on a couple of tests, so I was on probation there as well but somehow made it through. Luckily, today we have computers and word processors. It's just totally different.

Toby Chapman's Laboratory

Kleid

I picked a professor, Toby Chapman, who was brand new at Pitt. I think he got there the year before I arrived. He was interested in making peptides, but he also had a project on making DNA, actually synthesizing DNA was what he wanted me to do. When I interviewed professors to see which one I wanted to work with, I really got attracted to the DNA part because of that course I took from Gunther Stent. DNA seemed really interesting to me. Dr. Chapman was the only guy in the organic chemistry department who was working on DNA.

Hughes

You were at Pittsburgh from '68 through '72?

Kleid

That's right. So it would probably be 1969 when we chose which professor we were going to work with. In '69 I decided that DNA was what I wanted to work on.

Stent had told us in his course on molecular biology all about the genetic code, how that was sorted out, and how phages work. He said: "That's all understood now. It's really too bad you guys missed the really exciting part of molecular biology."

Hughes

He wrote a book to that effect. Gunther S. Stent, *The Coming of the Golden Age: A View of the End of Progress*, Garden City, NY: Natural History Press, 1969. [SSH]

Kleid

So here I am at Pittsburgh and I decide that DNA was the thing I'd like to study.

Hughes

That was a little unusual for an organic chemist, wasn't it?

Kleid

There were almost no organic chemists in the area of DNA, especially making DNA. Everybody in the literature was related to one particular guy, Dr. Gobind Khorana. Khorana's students had quite a few papers and had made quite a bit of progress. During the time I was in graduate school he got the Nobel Prize for solving the genetic code, which he shared with Marshall W. Nirenberg and Robert W. Holley.

Nirenberg did an experiment where he had an RNA polymer of U's [uracils] and showed that when he translated that in vitro he got phenylalanine. That was the conceptual breakthrough that allowed you to sort out the genetic code. So U-U-U coded for phenylalanine. What Khorana did was kind of take a sledgehammer to the project. He made every single possible combination of three letters in RNA and solved the genetic code and all the codons.

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DNA Synthesis

Kleid

Toby Chapman, who came from Elkin Blaut's lab, was interested in making new chemistry to synthesize peptides, and he thought that some of his ideas for making peptides might be applied to DNA molecules. He wanted me to try to link one nucleotide to another nucleotide, using a different kind of phosphate chemistry than was available at the time. So that's what I worked on for the four years. I was trying to do the chemistry of making DNA molecules.

Hughes

And how did his method--or probably by then your method--work?

Kleid

Actually, it was way before its time. The idea was to activate a phosphate so that when you added a hydroxyl group from the next nucleotide, it would join up and eliminate this active phosphate. Toby had worked on that with amide bonds where they had made active esters for making peptides, so he thought maybe we could [do] that with active phosphates. So I tried. I think the machines today that make DNA use that kind of concept. But back then it was just impossible--for me anyway.

Some of the problems were that you needed to keep everything absolutely dry. Every single molecule of water that was in your reaction tube messed it up so you really couldn't do it. We tried all kinds of dry boxes. And here we were in this old chemistry lab in Pittsburgh which was built at the turn of the other century, and it had no air conditioning and the windows were open. It was just humid as heck there all summer and cold and dry all winter long, so I couldn't get any of these reactions to work consistently.

Hughes

How much was Chapman involved?

Kleid

This was his first try at this kind of work, so he was just drawing on the blackboard different things to try.

Hughes

And you were having to go back to the lab bench and do it.

Kleid

Right. And at the same time take courses. And I was very involved with teaching because I was a teaching assistant--that's how I survived, with the paycheck. So there wasn't a lot of time. Graduate students don't actually have a lot of time to do research. I was very committed to getting out of Pittsburgh in four years. There are a lot of graduate students who last a long time but I wanted <u>out</u> of there very badly.

Hughes

Because you didn't like the area?

Kleid

The sun never shines in Pittsburgh; the winter starts on a particular day almost every year. Early November the snowflakes would start falling. It was just very difficult there. My bride and I, after a year there, saved up enough money to buy a Pontiac for $300. And of course it was stolen the first day. Luckily we got it back that same day. The rent was $100 a month and I was making $200 a month. It was tough.

Hughes

Was your wife in school?

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Kleid

Not initially. She worked in the sociology department at Pitt, so she was making a little bit to help out and taking some courses. She eventually got a master's degree in special education. We had a hard time in Pittsburgh, so we both wanted to go home.

Academic Challenges

Kleid

In about the third year of graduate school I was making it through all the courses except my grades were still just a little bit too low. The professors decided whether I would be in the Ph.D. program or whether I would end with a master's degree.

Hughes

Were they making any compensation for the fact that you were dyslexic?

Kleid

No, I never talked about it, and they never realized it. Nobody ever paid any attention to anything like that. In those days the judgement was you just weren't working hard enough.

Hughes

Which was not the case, was it?

Kleid

I was working my buns off!

The whole chemistry faculty met to discuss my situation. I was taking one course and my professor Toby Chapman and the course professor Foil Miller both knew that I wasn't going to get the needed B+ in that course. The vote was ten to ten to take up my case that day or wait until I finished this one course. The chairman of the department Dr. Wallace broke the tie and said, "Let's take up his case now." My professor said a whole bunch of nice things about what I was doing in the lab. Another professor, Dr. Sam Danishevsky, talked about how I was doing his organic chemistry course and a special night course he gave. The professor I worked for as a TA, Dr. Alfred Moye, said I was doing a really great job. Then this old professor, Dr. Henry Frank who discovered water structure at the turn of the last century I think, explained, "Sometimes scientists don't do that well in courses. I don't think that has much to do with being a good scientist." So they unanimously let me in the Ph.D. program. I got a C- in that course so I would have been out.

Pursuing DNA Synthesis

First Visit to Gobind Khorana's Laboratory, MIT

Kleid

A while after that my professor and I talked about what I was going to do next, after my Ph. D. thesis. I said that I would really like to do a postdoc in Dr. Khorana's lab. By that time his research team had followed up the work on the genetic code with synthetically making whole genes. They had made a gene that encoded a transfer RNA. It was about sixty or eighty nucleotide units long. It was a major project. Those people really knew what they were doing,

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so I asked Dr. Chapman if he could help me get a postdoc position there. Dr. Chapman helped arrange that, and I gave an interview at MIT, which is where Khorana was by that time. Originally he was in British Columbia and then he was in Madison, Wisconsin. After my talk about my trials and tribulations with active esters, Khorana said that he would consider me in his lab if I got a postdoctoral fellowship grant. He said he would be happy to sign his name on a proposal, so that's what I did.

In the three or four days I was at MIT on this trip and interview, I saw how they were making DNA. Even though there were a lot of publications on the chemistry, you don't see the equipment, how they were doing it, how they were watching out for the water--making sure everything was absolutely dry. They had all these different instruments and equipment to keep every single molecule of water away.

Hughes

Information you couldn't get by reading the articles?

Kleid

No, not the equipment part; I was using all the wrong things.

Graduate Thesis Project on DNA Synthesis

Kleid

I came back from that trip and said to Dr. Chapman, "Here's a project that I would really like to do: I'd like to make the DNA while its hooked onto a polymer and join nucleotides to nucleotides and use chemistry that was more like they were using at MIT. One of the ideas we talked about was getting away from active esters and doing the joining a more traditional way. I worked on that for the last six or eight months while in Pittsburgh.

The project in my Ph. D. thesis was on making T-T-T, three T's [thymidines] in a row. I think I spent about four or five months hooking T and T and T together. T.M. Chapman and D.G. Kleid, Oligonucleotide synthesis on polar polymer supports. The use of a polypeptide support, J.C.S. Chem. Commun. 1973, 193-194. Reprinted in *Benchmark Papers in Organic Chemistry*, Vol. 2, E.C. Blossey and D.C. Neckers (eds.), Dowden, Hutchinson and Ross Inc., Stoudsburg, Penn., 1975, p. 214. It doesn't seem like it would take that long, right? But it did. I wrote up and then defended my thesis on this plus a review on the methods used to make DNA that were in the literature at that time. D.G. Kleid, Synthesis of oligonucleotides. Dissertation Abstracts International B 33(8), 3555-B (1973).

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Kleid

I still remember the questions I was asked. One question was from Sam Danishevsky, who is now a very famous organic chemist. I think he went to Yale and then Sloan Kettering in New York City. His question was, "How do you know the difference between messenger RNA,

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transfer RNA, and ribosomal RNA?" This is pretty basic stuff. [laughter] So I did fine on the thesis, and then I went to MIT.

Postdoctoral Student, Khorana's Lab, MIT, 1972-1974

Colleagues and the Diester Method

Kleid

When I got to MIT I soon realized that I would be one of the token Americans in Khorana's group. It turns out that most everybody there were postdoctoral fellows from Europe and all around the world. He got his major support from government grants for the facility, materials, and things like that, but all these people brought their own fellowship money. It was just an incredible group of people. I was just so impressed and felt so lucky to be part of that group. One of the people that I got to know was named Kan Agarwal, (he was from India), and an absolute genius. He was a child genius.

Hughes

I noticed Agarwal's name on some of your papers.

Kleid

Right. He worked right next to me, and we became incredibly good friends. His family were not the traditional Hindu, because they ate meat. His parents were live-in helpers for a British family, and he and his brother were encouraged by this British family to go to an English boarding school. He got shipped away to school when he was just a little kid, and he never really went home again. Eventually, he made it to London and studied with some of the most famous scientists there are, and then got this position with Khorana in the U.S. He had been with Khorana for about ten years when I met him. So here was this kid about my age who in his whole life only knew science and school. But he was so interesting. I just totally enjoyed that guy.

Hughes

Did you end up collaborating?

Kleid

We did. He taught me how to make DNA. On his bench, I made my first DNA, which was twelve nucleotide units long. It took six months to make one oligonucleotide twelve units long. The sequence that I was making resulted from one of the very first DNA sequencing experiments ever done. In that lab they not only did chemistry of making DNA, they also developed the early methods of DNA sequencing. This was a little piece of DNA with a sequence from just past the coding sequence of a transfer RNA. Khorana and his group had decided, "With the transfer RNA's coding sequence, we're also going to make the DNA on either side of it." The goal of Khorana's group was to make a completely synthetic gene in the lab and in the test tube show that it functions.

Hughes

Were all these different people aiming at that very goal?

Kleid

Everybody in the lab, and there were about twenty. This project had taken already a couple years when I joined. So there were twenty or thirty postdoc years on this one project to chemically make a gene in a test tube and show that it works.

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Hughes

Was your experience using the solid-phase technique of interest to them?

Kleid

No. They had the methods they were happy with.

Hughes

The diester?

Kleid

Exactly. It was very slow and painstaking, but the DNA product at the end of the day was extremely pure. You could assemble all these pieces together to make this gene--but you had to have very, very pure DNA to do that.

Hughes

Nobody else at that time was making such pure DNA?

Kleid

No. Some of Khorana's former students were working on this at other universities, and they were trying new methods. Some were at that time competitors who thought they could make DNA a different way. In general, diester was the way to do it--no doubt about it at that time.

Gobind Khorana

Hughes

How much of a daily presence was Khorana?

Kleid

He was there every day, but he had a lot of people to tend to. We had lab meetings every week, and he would also have individual meetings with us. We would come in with our data and he would criticize how it was going.

Hughes

Was that intimidating?

Kleid

It was pretty intimidating. One of my experiments seemed perfectly okay to me, except the graph did not look smooth. There was some problem with the fraction collector in the middle of the night. In Khorana's publications I hadn't noticed that every figure was just perfectly symmetrical showing how nicely the oligonucleotide had come off the column. My graph line had this wiggly bumpy thing on the side--the graph line was not at all smooth. Dr. Khorana then explained to me that when he did this kind work he kept a cot in the lab so he could be there making sure everything went fine. I didn't understand that this result might not be so good. After I told Dr. Agarwal what had happened in my meeting. "You showed him that?! This bump--what's that? Oh, my god, you can't show him that! If he's going to publish this it's going to be embarrassing to him." All that had happened was that the fraction collector got a little stuck or something and that made the tubes not collect at exactly the right time. The result was a graph that wasn't smooth enough. I can tell you from then on my graphs looked a lot better.

Hughes

What is Khorana like as a personality?

Kleid

He was like a father to everyone in the lab--before I got there. It turns out that he is a professor beloved by dozens and dozens of his former students and many other people. But apparently a year or two before I joined the lab, the pressure of making this gene was very, very strong, and

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he had a nervous breakdown. When I worked with him, he seemed to have a bit of a feeling of paranoia about him. He was not the kind of person you would ever want to go out and have a beer with. So that was kind of stressful.

On seeing him about ten years later he seemed to me a completely different person. I imagine that the pressure to synthesize a gene and make it work had some impact on the way he acted.

Hughes

Yes, you caught him at a bad time.

Kleid

I guess. With the piece of DNA that I made, I had looked at the sequencing data before I started the project, and I didn't quite understand how they had gotten that particular sequence. Dr. Khorana assured me that this sequence was right. After spending about six months making this piece of DNA, Dr. Khorana explained to me personally that it turned out from more sequence data that the DNA I made was wrong. He said, "What would you like to do now?" (I kind-a wanted to do something different rather than go through that again. B. RamaMoorthy, R.G. Lees, D.G. Kleid, and H.G. Khorana, Total synthesis of the structural gene for the precursor of a tyrosine suppressor transfer RNA from E. coli, *J. Biol. Chem. 251*, 676-694 (1976).) He just gave me a ticket to do anything in his lab. I chose to learn about DNA sequencing.

Collaborating with Tom Maniatis at Harvard

Kleid

The lab was divided into organic chemists and molecular biologists who did the sequencing. So I said, "I would like to do the molecular biology," even though at that time he would rarely allow his organic chemists to switch to molecular biology. I think there was only one other person that made the switch. If you were in organic chemistry you stayed organic chemistry--but he let me switch over.

The lab made another piece of DNA for another project that had to do with the lambda bacteriophage genes. I made part of this piece of DNA with the help of a couple of other postdocs, Drs. Yuri Berlin and Valery Smirnov from the Soviet Union who also became very good friends of mine. Then I did a sequencing project, sequencing a little bit of lambda phage. K.L Agarwal, Y.A. Berlin, D.G. Kleid, V.D. Smirnov, and H.G. Khorana, The synthesis of a DNA duplex corresponding to the icosa nucleotide sequence at the 5' end of the messenger RNA from the Gene N of bacteriophage lambda, *J. Biol. Chem.* 250, 5563-5573 (1975). That was very exciting. That was way more interesting than the organic chemistry. In a sense, "God" had now given us the tools to read our own code. It was very compelling.

At the same time, Dr. Mark Ptashne's lab at Harvard was working on the same project. Tom Maniatis was his postdoc. They happened to sequence the exact same piece of DNA that I

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was working on. D.G. Kleid, K.L. Agarwal, and H.G. Khorana, The nucleotide sequence in the promoter region of the gene N on the bacteriophage lambda, *J. Biol. Chem.* 250, 5574-5582 (1975). T. Maniatis, M. Ptashne, B.G. Barrell, J. Donelson, Sequence of a repressor-binding site in the DNA of bacteriophage lambda, *Nature* 250(465):394-7 (1974). So we decided to collaborate. The collaboration was that I would take that little piece of DNA, the one I was working on at Khorana's lab, and move over to Harvard. So I switched from Khorana's lab to Harvard with that project.

Hughes

With Khorana's blessing?

Kleid

With Khorana's blessing and Mark's blessing. I took the grant that I had gotten and moved it over to work with Ptashne. Then we did more sequencing, and we developed another couple of methods to do that. T. Maniatis, A. Jeffrey, and D.G. Kleid. Nucleotide sequence of the rightward operator of phage lambda. *Proc. Natl. Acad. Sci. USA* 72, 1184-1188 (1975). We got deeper into molecular biology.

Hughes

What was the atmosphere of Ptashne's lab?

Kleid

It was completely different, as you might imagine. I moved to a lab that was mostly graduate students and one other postdoc, and that was Tom Maniatis. So we were the two postdocs and all the rest were very bright young graduate students. They were all struggling to learn everything there was to know about how proteins bind to DNA and what sequences they like--in particular, the lambda repressor and how the lambda repressor finds its piece of DNA, the lambda operator.

Early DNA Sequencing

Kleid

My job there was sequencing. I worked on the sequencing of all kinds of mutants of the lambda operator that interfered with the binding of the repressor so we could try to figure out what the repressor liked about that DNA sequence. So we sequenced these mutants, and as a result had a lot of theories on what was going on there. T.

Maniatis, M. Ptashne, K. Backman, D.G. Kleid, S. Flashman, A. Jeffrey, and R. Maurer. Sequences of repressor binding sites in the operators of bacteriophage lambda. *Cell* 5, 109-113 (1975). B. Meyer, D.G. Kleid, and M. Ptashne. The lambda repressor turns off transcription of its own gene. *Proc. Natl. Acad. Sci. USA* 72, 4785-4789 (1975).

Hughes

Sequencing in those days was a very tedious procedure, was it not?

Kleid

It was.

Hughes

What was holding your attention, assuming that it was held?

Kleid

What was holding my attention was the data of course. Once you figured out the sequence, what was in there, what was the code? The genetic code concerns translation of RNA to make proteins. So what codon corresponds to which amino acid? But here we were looking at the code for promoters and operators, the sequences that start and stop transcription. We were looking at the next level of sequencing: What was in that DNA promoter sequence that RNA polymerase liked? It was the next level, and it was not that simple. Our group and Wally Gilbert's group and other people around the country sequenced a number of promoters and as a result we were starting to get a collection of sequences for these promoters. Then the simple idea was, well, just line them up and read the code now. But that was pretty difficult to do. The sequence data all by itself didn't give the answer, plus the sequencing itself was way more difficult at that time.

What we did was called the wandering spots sequencing method. You took a DNA and labeled it at one end and then you broke it down with chemicals so that it was either one, two, three, four, five, up to maybe twelve or fifteen nucleotides long. More commonly at that time we could start with a primer and elongate with one of the missing nucleotides, or a very small amount of it, so you got a whole population of DNA molecules that were from one or two to fifteen nucleotides longer than the original primer.

Then you would separate those by charge using electrophoresis, and then transfer that separation to cellulose, and then use another way to separate by size called homochromatography. You would see these little wandering spots going up the autoradiograph as the little piece of DNA got shorter and shorter. The longer stuff stuck on the bottom and made some spots, then the spots went up and to the left and right, and left and right, and up. I think one of my papers has a picture of those wandering spots. T. Maniatis, A. Jeffrey, and D.G. Kleid. Nucleotide sequence of the rightward operator of phage lambda. *Proc. Natl. Acad. Sci. USA* 72, 1184-1188 (1975). It takes about two weeks to actually get some data. So you get fifteen nucleotides in a couple of weeks, and then you'd have to read it three or four times or get the sequencing data from both directions, to really figure out what the sequence was.

Hughes

Was this the Maxam-Gilbert method?

Kleid

No. That wandering spots method came before the Maxam-Gilbert method. When I came to Mark's lab I was working on this wandering spots sequencing method that was partially developed by Dr. Fred Sanger's laboratory in England and in Dr. Khorana's lab. Tom Maniatis was using it in his project before I joined Ptashne's group. We taught Alan Maxam, who worked with Wally Gilbert, how to use that method.

Actually, the wondering spots in a way led to the Maxam-Gilbert sequencing concept. One day another Russian, Andre Merzibekov, came to visit Wally Gilbert's lab and Mark's lab. The laboratories were just about right over each other on two floors in a building called the Harvard Biolabs. The labs held seminars together quite often. This Russian guy did chemistry on DNA molecules and noticed that you could break DNA molecules at G's [guanines] using a particular chemical called "DMS" and some other treatments. When radiolabeled at one end you could use that DNA in the wandering spots method if you did a partial reaction only

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breaking the DNA at random sites to get a collection of different-length molecules. But if you instead ran a gel electrophoresis size separation, you could see a lot longer pieces and it looked sort of like a little ladder with rungs missing. Much like the wandering spots you would see a collection of molecules, but instead of spots you would see bands separated by a certain distance. That distance would be from the start of the molecule, the labeled end, to the first G, and go a little longer to the next rung, and that would be to the next G, and then a another rung would be the next G, and so on. So you could see this kind of ladder where spacing was dictated by where the G's were in the sequence. In the spaces would be where the As [adenines], Ts [thymines], and Cs [cytosines] are, if you could reveal those by some other treatment.

Alan and Wally said, "We could probably do that to the other letters. Maybe we can make a chemical that can break the chain at A's, and then maybe at C's and T's, and then run that side-by-side on a gel and see how that looks." And they did that. I still have a copy of the very first gel where they did Gs and Cs. Very soon after that we tried this in Mark's lab. In fact, I think one of the first few Maxam-Gilbert type sequencing gels published is in one of my papers. D.G. Kleid, Z. Humayun, A. Jeffrey, and M. Ptashne. Novel properties of a restriction endonuclease isolated from Haemophilus parahaemolyticus. Proc. Natl. Acad. Sci. USA 73, 293-297 (1976). [note: This paper contains a very good example of a dyslexic experiment. The plan was to treat the DNA with the restriction enzyme, label the ends, and then use the Maxam-Gilbert type sequencing method. Instead, I did the Maxam-Gilbert treatments first, then cut the DNA and labeled the ends. I figured, what the heck, it should still work. When I ran the sequencing gel it took me two days to figure out the crazy results I got. The restriction enzyme would not cut that population of the DNA fragments that had been treated with the DNA sequencing reagents if they reacted at the sites in the DNA sequence that the restriction enzyme required for activity. In this publication I repeated this dyslexic reverse experiment on purpose. In this study we proved that this particular restriction enzyme recognized a sequence quite far from where it cut. A few years later this technique was deemed "footprinting." D.J. Galas and A. Schmitz DNA footprinting: a simple method for the detection of protein-DNA binding specificity. *Nucleic Acids Res* 5, 3157-70 (1978).]

Alan Maxam was a good friend of mine. So I was there to see the whole DNA sequencing technology that broke through at that time. Dr. Frederick Sanger had a slightly different method. It was more like the wandering spots method with a gel. They used a primer but then did the elongation reaction four times using limiting amounts of G, A, T, or C and then ran them side-by-side together on a gel. The new conceptual thing with these new sequencing methods was really the gel, I think.

Going back to Khorana's lab for a second, I want to mention a few of other people that had an influence on me. One was Dr. Marvin Caruthers. In the early 1980s Dr. Caruthers helped start Amgen. Like Kan Agarwal, who was the central figure or dominant scientist in the organic group, Marv Caruthers was a major figure in the molecular biology group. I think those were the two dominant scientists among quite a few

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very, very ingenious people. Dr. Amos Panet In the mid-1980s Dr. Panet helped Biotechnology General become a significant company. was one of those, and we did a project together with another Nobel prize winner, Dr. David Baltimore, W. Haseltine, D.G. Kleid, A. Panet, E. Rothenberg, and D. Baltimore. Ordered transcription of RNA tumor virus genomes. *J. Mol. Biol.* 106, 109-131 (1976). and the then postdoctoral fellow, Dr. William Haseltine. In the 1990s Dr. Haseltine headed up Human Genome Sciences. We did several projects together during the 1970s including one with Dr. Gallo: M.S. Reitz, F. Wons-Staal, W.A. Haseltine, D.G. Kleid, C.D. Trainor, R.E. Gallagher, and R.C. Gallo. Gibbon Ape Leukemia Virus - Hall's Island: New Strain of GALV. J. of Virology 29, 395-400 (1979). [pause] So that was my career on the East Coast.

Hughes

A theme is that you were getting deeper and deeper into molecular biology.

Kleid

That's right. I was trying to help figure out how restriction enzymes cut DNA and how other proteins bind to DNA. My actual hands-on was always tied to DNA though, first trying to figure out how to make DNA, and then on to synthetic DNA, and then using primers in sequencing DNA. The last step was cloning DNA. It turned out that you needed those three steps in order to make genetic engineering into a practical technology; you needed to be able to synthesize DNA; you needed to be able to clone it; and then you needed to be able to see what you made.

Advent of Recombinant DNA

Herbert Boyer's Seminar at MIT

Hughes

Well, let's go to the cloning because in the period when you were a postdoc the Cohen and Boyer cloning papers were published. Do you have a story about that?

Kleid

Yes. I remember the first time I saw Herb Boyer. He gave a seminar at MIT, and he visited Khorana's lab and Malcolm Gefter and other people at MIT. He might have also given a separate seminar at Harvard or it was joint. MIT and Harvard were just down the street from each other, so often the seminars that had a major guy were attended by scientist from both.

Hughes

Do you remember which year? You were at Harvard 1974 to 1975.

Kleid

I was at MIT 1972 to mid-1974. What was the date that Herb went on his first tour?

Hughes

The first Boyer-Cohen paper was published in November, 1973. Boyer began talking about the work at least as early as the previous June because he mentioned it at the Gordon Conference on Nucleic Acids. The Singer-Soll letter arose from that conference which eventually led to

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Asilomar and the recombinant DNA guidelines and all that. So it could have been in 1974 that Boyer gave a talk at MIT or Harvard.

Kleid

There was a controversy about it already, because I remember there were questions or something at the end about what the implications were. So it could have been after that Gordon conference.

Hughes

Controversy about the potential biohazards?

Kleid

Yes. A number of people were very nervous about cloning human fragments of DNA. I don't know who started the controversy, but I don't think in those days you could have given a talk without mentioning it--especially Boyer. He gave this talk which was basically about the Boyer and Cohen plasmid experiments.

Hughes

Was this a seminar or a larger gathering?

Kleid

It was just a seminar, but I think they got a bigger conference room. It was very highly attended.

Hughes

Boyer talked mainly about the science?

Kleid

Yes.

Hughes

Do you remember him saying anything about potential commercial application?

Kleid

No. It was about plasmids that you could use, and the selection markers, and how interrupting a marker could be useful. It wasn't pBR322 yet; it was pMB9, one of the earlier vectors. I'm not even positive if it was pMB9. But it was basically for *E. coli*, making plasmids, cutting the pieces of DNA, and showing you could create plasmids with different antibiotic markers.

Hughes

The audience was strictly scientists?

Kleid

Oh, yes.

The Controversy Over Possible Biohazard

Hughes

Were there any big names dissenting? I'm thinking of George Wald, the Nobel Prize winner, and his wife Ruth Hubbard. Were they already aware of recombinant DNA and attending seminars like this?

Kleid

They came slightly after, as I recall, because this was just the seeds of an issue. By 1975, when I was back in California again, the big controversy was when Wally Gilbert and Mark Ptashne decided they were going to need a special cloning lab at Harvard; they were going to do some of the experiments that Herb Boyer was talking about, and then they ran into this controversy. I think it was '76, '77 when those people came to the fore.

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Exciting Scientific Possibilities

Kleid

In the very beginning it was all just very, very fascinating. I don't think anybody predicted that there would be any controversy because you were just talking about cutting and pasting DNA together.

Hughes

Were you excited about it?

Kleid

Oh, absolutely!

Hughes

Were the possibilities immediately apparent to you?

Kleid

The possibilities of learning more about how DNA works.

Studying Enzyme Restriction

Kleid

At Khorana's lab we studied restriction enzymes with synthetic DNA pieces. One of the other graduate students made a piece of DNA that happened to have a restriction site in it and reacted that with these restriction enzymes to see how they were working. One of those enzymes actually came from Herb Boyer, as I recall. I think it was EcoR1 that we studied even at that very early stage. Herb Boyer had known Dr. Khorana from before--I don't know how. Khorana was good about getting materials from different people and studying how they worked on DNA. This was exactly what Herb Boyer was interested in, how these enzymes functioned.

Hughes

Apparently Boyer was very generous about giving out his enzymes.

Kleid

Absolutely. And with his plasmids too. In fact, that started it all in my mind. Molecular biology at that time would not have been possible without a tremendous amount of cooperation between scientists, because you would trade your restriction enzyme or polymerase or ligase or plasmid so that you wouldn't have to make everything. It was a golden era of molecular biology.

Hughes

Did Stan Cohen enter into this exchange?

Kleid

I don't recall. Personally I didn't have that much contact with Stanley Cohen. I don't know why.

Hughes

Golden age of molecular biology--

Kleid

Yes, just like Gunther Stent's time. Only Gunther Stent missed it because he went into nematodes.

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Reagent Exchange

Hughes

We're jumping ahead, I know, but that easy exchange of materials among scientists is not so easy anymore. Do you want to comment?

Kleid

But the exchange isn't as needed. Nowadays you can buy these enzymes and DNA at the DNA store. There are catalogues filled with all these enzymes. It's just a completely different issue. Back in the seventies you wanted to learn how this DNA is working: What are these promoters? What's causing them to be sites for RNA polymerase? How do these genes work? That was the issue. Plasmids were a new tool you needed in order to work on that. Think about Khorana's idea: let's synthesize the complete gene in the test tube and then see what happens. That was impossible then without a lot of help. It took thirty, forty postdoc years just to make the DNA, and then in using the assays to see if the DNA was any good--and then it was gone, used up in the tests. All of a sudden you could clone that DNA.

The first cloning of a synthetic DNA was with Herb Boyer working with Drs. Art Riggs and Saran Narang, (Dr. Narang was one of those former student-competitors of Khorana that we were talking about). They had synthesized the DNA that encoded the lac operator, and Art Riggs had spent his life studying the lac operator. So they made a synthetic DNA and then cloned it. Now you had enough so you could study how that DNA worked.

The Genentech/City of Hope Somatostatin Project

Hughes

Do you know how Riggs learned recombinant DNA technology? In those early days, how was the technology disseminated?

Kleid

In this particular instance, they all worked together. Dr. Narang made the DNA with one of his students, Dr. Itakura, and they brought that DNA to Art Riggs. Art Riggs was working with Herb Boyer, and so they made a plasmid with the help of Herb's group that included Drs. Herb Heyneker and Paco Bolivar.

Hughes

So that part of it was happening in Boyer's lab.

Kleid

Right. Boyer's lab and Art's lab. I think the cloning aspect was mostly in Boyer's lab, and it involved Herb Heyneker and Paco Bolivar and Ray Rodriguez. They were trying to develop a plasmid that was really handy for cloning that would have two markers. The ones that they chose eventually were for ampicillin and tetracycline. They constructed these plasmids so they weren't so unwieldy, because the original plasmids were very big and had lots of pieces when treated with restriction enzymes. So they whittled it down so it would be a lot easier to work with, and pBR322 by the late 1970s became the standard workhorse.

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Plasmidology

Hughes

Was the Boyer lab the center of plasmid development? Were there other laboratories also trying to develop vectors?

Kleid

Not that I can recall. He wasn't really the center, but he was kind of the center from which the technology got disseminated. Just an example of what I mean: In Ptashne's lab when I was there there was a graduate student, Mr. Keith Bachman, who came to Boyer's lab in '74-75 and learned about the vectors and then took samples of them back to Mark's lab and started working on those same vectors at Harvard. That work was part of his Ph. D. thesis. He eventually became a postdoc in Herb Boyer's lab and even worked a bit with Genentech when it first started; he never actually worked at Genentech, instead he continued at U.C. Med Center. Anyway, Keith Bachman was, along with quite a few other postdocs, working on the next generation of plasmids after pBR322, so-called expression vectors. Others were working on vectors for other types of bacteria and yeast cells. But still, I would also say that Boyer's pBR322 got so widely disseminated and used (and it just worked perfectly) that it became such a standard that it was the end of the story. In a sense, *E. coli* cloning vector plasmid development was done in 1978. We still use it today.

Stanford Research Institute

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The Job Hunt and Hiring Process

Kleid

So here I was at Harvard and it was really time to come home to California. I'd been trying to do that ever since I went to Pittsburgh. I had written for jobs and I had interviews at places like Syntex and a couple of other smaller companies on the West Coast.

Hughes

Why had you decided to go with a company rather than a job in academia?

Kleid

Academia has an awful lot to do with trying to raise money for your research. It just takes so much time and effort to try to do that particular part. And the universities were filled with molecular biologists. They had all they wanted because molecular biology was not that interesting to most of the universities at that time; it was just starting. They didn't have molecular biology departments; you were in organic chemistry or you were in biology. There was very little in the way of faculty positions in molecular biology except at the major schools, and they had their molecular biologists--and they were good. So, there weren't going to be any professorships out there for me, especially in northern California since I only had Berkeley to choose from, and I barely even graduated from there. I couldn't imagine being part of their department. [laughter] It was full of Nobel prize winners. They would look up my grades; that would be the end of it. So I thought that the industrial area would be a better fit--if "industrial molecular biology" only existed.

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A Project on Anti-cancer Drugs

Kleid

I had written to Stanford Research Institute, SRI International now. I interviewed a person who worked there and that seemed like a really good fit for me because it was in between industry and academia. It wasn't an academic position, but you did research and you usually got your money from the government or from other companies. After my interview, I wrote a letter to them, and a year passed, and so I went and visited him again and really begged for a job.

Hughes

This was the head of SRI?

Kleid

No, this was the head of life sciences at SRI. His name was Dr. David Henry, and he worked more in organic chemistry. At the time he had a very large project on anthracyclines for cancer, the same ones we use now. He studied adriamycin and related anti-cancer drugs. These drugs work by binding to DNA and putting cells out of action by destroying the cells' ability to replication their DNA. So I felt there was a little fit there because I thought we should be studying DNA and this activity at the sequence level. I thought, well, nobody has really taken a look at how these anti-cancer drugs damage the DNA and change its sequence. Maybe we can take a look at that. I thought there would be some interest in that because the largest granting agency was the National Cancer Institute (or NCI), part of NIH.

I didn't think SRI was very much involved with molecular biology up to that point in time. Here was cancer and DNA and sequencing. So I convinced them that I could come up with some grant proposals doing that. So Dr. Henry said fine as long as I brought my grant with me. So I came with my grant. There was six or ten months of it left. I asked Mark Ptashne if I could take my grant to SRI. And he said it was okay. I guess it was up to $300 a month by then. So here I am, graduate student, Ph.D., three-year postdoc, and finally a real job--$300 a month, fine.

Mark Ptashne and Tom Maniatis

Hughes

Before you leave the East Coast give me a sketch of Ptashne.

Kleid

Mark was the youngest full professor at the time at Harvard, the youngest they had ever had in science. He is a very short guy. He had a little bit of a Napoleon complex. Some people have big egos and they're always telling you how wonderful they are. Well, his ego was so big he didn't have to tell you how wonderful he was because he knew you already knew it. [laughter] He was just an incredible person to work with.

Hughes

You mean incredibly good?

Kleid

Incredible. His lab was top-notch and people in there were extremely good. His vision of science was very, very interesting. He was trying to figure out how DNA works, starting with a very narrow little system, lambda operators and lambda repressors. He felt that that particular system was all you really needed to know about molecular biology. That was the only thing he

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ever worked on from the seventies through the 1990s. I think he's at Sloan-Kettering now in New York City. But throughout his career at Harvard that was pretty much the only thing he ever worked on. He thought it was the most interesting thing to work on. He just really studied the details of the details in that little system. The more detailed your understanding the more questions would reveal themselves was his reasoning I guess.

His postdoc, Tom Maniatis, was one of the stars of the Harvard Biolabs. Everybody came to Tom for advice on how to do everything. Every new experiment they did, everybody migrated to Tom because he could explain to them very succinctly and very crisply, "Do this, this, and this." He gave them directions and off they'd go. He was a guru of the Biolabs. And in contrast here I was, the other postdoc, and I came from a chemistry background whereas Tom came from molecular biology. Tom had a huge following at Harvard, and my experiments didn't work that well, and I couldn't write that well.

One day Tom wasn't in his lab and somebody came in to get some advice. I was sitting there, and he asked a question. I happened to know the answer. So I was sitting in Tom's chair, writing the notes out for this guy, and Tom came in, and I was taking his place. This was really bad. I think from that time on he really didn't treat me that well.

On the other hand, I felt that Tom was such a dominant force, especially among Mark's graduate students, that they weren't actually learning to be scientists. They were leaning on him for every single thing, and they had been in Mark's lab for a long time. Some of them had been there for three or four years without even being close to finishing. So I was pretty happy when Tom moved on. And he was probably very happy to do that too. He went to Cold Spring Harbor, and then he went to Caltech, and then he ended up back at Harvard again. He's one of the main scientists there. He and Mark started up one of Genentech's competitors, in my mind a copy-cat company, Genetics Institute, now part of Wyeth.

Hughes

You certainly met high-profile scientists.

Interaction with UCSF and Stanford Scientists

Kleid

So I came to SRI. One of the first things I did was to look up Herb Boyer--well actually one of his postdocs, Herb Heyneker, whom I met in one of those scientific meetings. Some of my fellow scientists at SRI and I would every three or four weeks or so come up from Stanford Research Institute and go to seminars at UC Med Center. We did the same thing at Stanford. In fact, there got to be a little crew of us at SRI who would go to the seminars and be part of the academic community at Stanford and UC Med Center, so we weren't just isolated at SRI.

Hughes

Which seminars were you going to at Stanford?

Kleid

There was a professor there that we knew that would invite us to seminars. I haven't thought of these names in a long time.

Hughes

Do you remember the department?

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Kleid

I think it was biochemistry. It could have been one of my friends from SRI knew somebody, and that's how we got started there.

Hughes

The biochemistry department at that time was a hotbed of activity on DNA.

Kleid

Absolutely.

Hughes

You were in the right place for DNA research. Did you realize when you went to SRI that you'd be where it was happening in terms of recombinant DNA?

Kleid

Yes. That was one of the reasons I wanted to come back here so much. My project was on DNA, and I was born and raised here. We interacted as much as possible with Stanford and UC Med Center.

Establishing a Laboratory at SRI

Hughes

Did you have to set up a laboratory at SRI?

Kleid

Right. My lab started out being about 20ft. x 40ft. long with one cleared bench with lots of drawers, all absolutely empty. "Here you go. Here's your lab."

Hughes

Did you find that intimidating?

Kleid

It was tricky because you had to start from scratch. SRI had places to buy some instruments and labware. There was also leftover labware. So I put together what I thought I needed. That early part of what I wanted to do was about chemicals binding to DNA and DNA sequencing, so I started off getting the original Maxam-Gilbert sequencing thing going.

Hughes

Were you on your own? Nineteen-seventy-five is when you arrived.

Kleid

Right. I was completely on my own. I was in Dave Henry's department where most of the people were organic chemists. They were working on anti-cancer drugs and analogs. So my area, DNA, was going to be completely new. One of the things I was going to do, and eventually did, was to clone some synthetic DNA's to be substrates for these chemicals because I wanted to have a little sequence that I knew exactly what it was. The idea was that we could take that little sequence, react it with the drug, put it into a plasmid, and then cause the plasmid to get replicated, and see how did it repair itself.

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Biosafety Issues

Kleid

If you had a drug bound to it, the question was: How was it going to fix that? So I wanted to clone a known sequence of DNA. To do that, I needed to have a biosafety committee at SRI. It took a year to get permission to clone the lac operator.

Hughes

Did SRI have a biosafety committee?

Kleid

No, I had to start it. In order to do recombinant DNA under the NIH guidelines, your institution has to have a biosafety committee. I went to SRI's safety group that handles this sort of thing and we put together a biosafety committee and got members from inside and outside. Then one of the vice presidents at SRI--I don't recall his name--said in effect, "What are we doing this for? We don't want to do recombinant DNA; that could be dangerous. It's also controversial. We got into this kind of problem when we worked on chemicals involved with warfare" or something like that. In the Vietnam War era SRI worked on a project for the defense department, and there were marches and the protesters almost shut the place down. This guy says, "We don't want to do that again; we're going to have marches all over the place." We were just cloning the lac operator for crying out loud.

We eventually got the biosafety committee set up so I could do what I wanted to do. By that time I did get some grants to do it. I wrote a grant that went to the NIH granting agency and I tried to ask the kind of questions they were interested in. It just worked perfectly. I spent a lot of time on that.

Hughes

SRI must have been considered more academic than industrial, because, as you probably remember, the NIH guidelines only applied to academia.

Kleid

Or anybody working under an NIH government grant.

Hughes

Oh yes, that's right.

Kleid

If you wrote a grant that used recombinant DNA, you had to submit your plan to your own institution's biosafety committee. We had to jump through those hoops.

Hughes

Was it smooth sailing once the committee was organized?

Kleid

Once SRI management capitulated it was fine. The first biosafety committee was helpful in that regard. But it wasn't warm and fuzzy.

Hughes

They were still nervous?

Kleid

The management was, but the biology section was perfectly happy. SRI wanted to get into this DNA area. The organization was, at that time anyway, a bit difficult. I always thought at the time, if you could make it at SRI, you could make it anywhere. You weren't going to have a guaranteed salary; it all came from grants--a total soft-money place. So you had to raise the money for your research--completely.

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Hughes

You told me that one of the reasons you were interested in industry was so that you didn't have to write grants.

Kleid

I know. So here I am, spending all my time writing grants. And as I told you, I don't write very well. It takes me forever. Although they didn't have any word processing computers yet, they had a wonderful thing called editors. So I would do my best to scribble my stuff down and hand it to people who did know something about writing. They fixed it all up and typed it. I took advantage of that and wrote three or four or five grants while there. Once the grants were funded I was able to hire some fellows to help me.

Arrival of John Little and David Goeddel

Kleid

One of the postdoctoral students who came by asking about a job was John Little. John was from Stanford and I had met him there. He was a molecular biologist and he knew all about how to clone DNA using plasmids. I had been in the DNA part. I didn't do that much in actually cloning and looking for plaques and picking colonies. So he came to my lab and he worked on that part and I think did a fine job.

About six months or a year after John Little joined, I got a call from Marv Caruthers telling me that he had this graduate student, Dave Goeddel, who was just finishing his Ph.D.and wanted to come to California. Marv raved about how bright he was and what a good job he did as a graduate student. Dave wanted to come to California because it would be close to Yosemite. He was a rock climber first and a genius science student second. As a graduate student he did his projects extremely well. The University of Colorado has these rock formations right outside of Boulder. Dave spent a lot of time climbing these rock formations. He became an excellent rock climber. When he came to SRI his main goal was to have a job that was close enough that he could go to Yosemite whenever he wanted and climb rocks. So that's what happened.

While Dave worked at SRI he climbed El Capitan, and that's a one week thing. He explained to me how he does this: you have a rope, and you get a certain distance, and after about a day your rope doesn't reach the ground anymore, and you can't go back down. You have to go up. There's no way to go down. You must complete the trip. If you get nervous, your fingers sweat, you fall right off. So you have to be absolutely focused and confident and just climb that rock. It was just amazing to me that somebody could have a personality that would be interested in doing that.

Hughes

Did you ever see him do it?

Kleid

I went with him to the mountains a few times, and he did some rock climbing on big boulders. I didn't go to see him climb El Capitan or anything like that.

Dave was very talented at this and he had all the equipment. I recall that he told me that he met his future wife because she saw his picture on a poster in one of these climbing shops and said, "I want to meet that guy." She found him and she married him.

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Hughes

Isn't that a story!

Kleid

Carol is her name. She was just like Dave, just totally committed to whatever they were going to do. It was amazing to see those two. They were so alike; they were like brother and sister.

Anyway, Dave came to my lab, and he learned the details of cloning: pouring the plates, transformation, growing of the colonies, picking colonies, and analyzing the DNA sequences.

Hughes

Which he hadn't done at Colorado?

Kleid

No. He was mostly on the DNA synthesis part. They did some biochemistry but not so much in cloning. At about the time Dave came to SRI, one of his former fellow graduate students, Eric Kawashima, synthesized the DNA encoding the lambda operator Kawashima, E., Gadek, T., Caruthers, H.M. *Biochemistry* 16, 4209-17 (1977). While in Caruthers's laboratory Dave and another of Caruthers's graduate students, Dan Yansura, did the lac operator. Eric made the lambda operator DNA and he sent this DNA to us at SRI. Using the techniques that Dave had learned from John Little, we cloned the lambda operator. Our work on this has never been published. It was just before we came to Genentech near the end of '77. Dave was in my lab for about a year and he overlapped with John Little for about six months.

Hughes

In that year were you working closely together or was he doing his thing and you were doing yours?

Kleid

We had one lab. By this time the lab was outfitted pretty well. I had raised up a notch. I had gotten my grants, so SRI gave me a bigger room with nice benches and we just had them all painted. So we were in really good shape, with John Little and a technician too, so there was four of us. I did some experiments, but not really that much. I was still working on raising the money, writing the grants. I was not hands-on anywhere near as much as Dave. Dave and John had total time just to work in the lab and do experiments all day long. I really wanted to do the experiments, but they were having so much fun, they would hardly let me help.

At that stage Dave really had a good, solid knowledge of what to do, and he kept very good notes and nice directions.

Hughes

Was he working on DNA repair?

Kleid

That was the plan, but the first step was cloning the gene so we'd have a target, and we also did some studies on the binding of the drug. When the drug bound the DNA between the base pairs, it actually unwound the helix a bit. One of the interesting things that Dave Henry had worked on was two drugs hooked together. When you link together two chemicals that both bind to DNA and they bind extremely tightly. We were studying how those DNA binding drugs unwind the DNA. So we were doing experiments on that as well as cloning little pieces of DNA.

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II Genentech, Inc.

The Somatostatin Project

Hearing about Somatostatin

Hughes

How did you hear about Genentech?

Kleid

Well, I told you that we used to go to all these seminars. One of the scientists I saw fairly often was Herb Heyneker. Herb and I, and his wife and my wife, became good friends. We went out with them a few times. Herb talked a bit about the somatostatin project that he was working on and how they made these DNAs. He was working with Art Riggs. That was really interesting. He was absolutely so excited about that. Then he talked about this Genentech company that they had formed and that company was funding this project. I went up to Herb Boyer's lab and visited with him a few times. As you can see our research was sort of along the same lines, at least it used some of the same techniques and tools. They were cloning synthetic DNA for somatostatin, and we were doing lambda operator. There weren't very many people in the world cloning synthetic pieces of DNA--there were almost none. So we had a lot in common. We needed the restriction enzymes too, and we needed other synthetic DNA pieces, so we were trading those around, because we hadn't actually made any DNA at SRI.

Richard Scheller's DNA Linkers

Kleid

One of the other people we met along the way was Richard Scheller. Scheller was making synthetic DNA's that had restriction sites in the middle. See the ROHO oral history with Dr. Scheller. [SSH]

Hughes

He was at Caltech.

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Kleid

He was at Caltech, and he was also helping Genentech. He made little linkers that Heyneker was using in the lac operator project and might have wanted to use with the somatostatin DNA project. Previously they synthesized the lac operator and put linkers on the end. Those came from Richard Scheller. Scheller was going to synthesize the whole somatostatin DNA gene. Instead Keiichi Itakura took over and made those pieces. Scheller spent a lot of time making the very first somatostatin DNA piece and didn't quite finish it all. So it was just one DNA part and then another smaller DNA part, and then that could be joined together to make a little DNA with a restriction site. He made that, and then Art Riggs took those pieces of DNA up to Herb Boyer's lab and spent a lot of time learning cloning himself. That's how he got the hands-on experience with Heyneker.

Heyneker likes to tell the story of how Dr. Riggs cloned the *Bam* linker. Heyneker says, "Oh, that's all Art could do; he cloned the *Bam* linker." So later, with Dr. Itakura's DNA encoding the somatostatin, Herb Heyneker joined the pieces of DNA together, and with Paco Bolivar they were the ones that completed the cloning of somatostatin.

Hughes

Scheller is the name that drops out of most of the accounts. I noticed he's not on the somatostatin paper. Contributing the linkers isn't enough to make you an author? Of course he was a graduate student.

Kleid

He was a graduate student. He got thanked for those pieces of DNA and he is on the paper describing the original use of the linker. He had given the linker out to a lot of people. What he used to do was to have a piece of filter paper and squirt a little sample of the linker on it and mail it to you. So he got on a lot of papers by doing that, mostly being in the thank-you section.

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Kleid

The somatostatin gene was designed with *Eco*R1 restriction site on one end and *Bam* on the other, so in the final plan they didn't use the linkers on the somatostatin project. But if you look at the lac operator cloning project, the one that came before, that one used linkers.

Hughes

I, maybe wrongly, associate Scheller with the somatostatin project.

Kleid

He made one or two of the pieces of DNA that they were going to use to do somatostatin, but those pieces of DNA didn't work.

Hughes

Why?

Kleid

Turn off the tape recorder and I'll show you. [tape interruption] I happen to have Richard Scheller's notebook from Caltech here in my office because we were using this in a litigation about ten or fifteen years ago and we actually never gave it back to him. [laughter]

Hughes

Now it comes out.

Kleid

I had fished it out because I was going to give it back to him a couple weeks ago. This has his first experiments from 1975 all the way through to him making the piece of somatostatin DNA. I'm sure that he'll be interested in seeing this again.

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New Emphasis on Keeping Notebooks

Hughes

That notebook of course comes from the period when he was a graduate student at Caltech.

Kleid

Right. He wasn't that good at writing his name and date on the pages here.

Hughes

That's significant, isn't it? The notebook dates from a time before people were so conscious of intellectual property claims.

Kleid

Right, they weren't conscious of it at all then, and they still don't do this very well. [laughter]

Hughes

Say you as a patent agent.

Kleid

I have looked though enough notebooks, especially those from Genentech, where the directions for how to keep a notebook properly are right in front of the book. How many people actually keep a good record? Not many. I happen to have my own 1978 notebook right here too and you can see the absolute opposite. [chuckles]

More on Early DNA Synthesis

The Diester and Triester Methods

Kleid

Anyway, back to the Richard Scheller story. He synthesized these synthetic DNA's. I met him on one of his trips up here to see Herb Boyer's lab. Anyway, this was just kind of cross-fertilizing that happened in Boyer's laboratory. The very few people that did cloning of synthetic DNA molecules at the time all got to know each other.

Hughes

There were the people that Khorana had attracted, weren't there?

Kleid

They came there too. Dr. Khorana's lab did an experiment on the cloning of the transfer RNA that was being made while I was at Khorana's lab in the early seventies. In the late seventies, after the lac operator was cloned, they decided to go ahead and clone the DNA that they made. Brown EL, Belagaje R, Ryan MJ, Khorana HG. Chemical synthesis and cloning of a tyrosine tRNA gene. *Methods Enzymol.* 1979;68:109-51. I don't think it was the original concept to do this because, as I said, the concept was to chemically synthesize the DNA and show that synthesized DNA worked in the test tube. Khorana HG, Agarwal KL, Besmer P, Buchi H, Caruthers MH, Cashion PJ, Fridkin M, Jay E, Kleppe K, Kleppe R, Kumar A, Loewen PC, Miller RC, Minamoto K, Panet A, RajBhandary UL, Ramamoorthy B, Sekiya T, Takeya T, van de Sande JH. Total synthesis of the structural gene for the precursor of a tyrosine suppressor transfer RNA from *Escherichia coli*. 1. General introduction. *J Biol Chem.* 251(3):565-70 (1976). But

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here with cloned DNA, you were using biology to replicate it. In Khorana's eyes it might seem to be kind of a cop-out; you're not really using the chemistry anymore. But let's go ahead and clone it. And they did, and they ended up learning a lot about that particular DNA and how it works by going ahead and studying the cloning of it. They cloned the DNA molecules that were made by the diester method. That's the big difference between Itakura-Narang-type DNA used by Dr. Rigg's which was made using the triester method.

Now the trouble with the triester-made DNA is that it's not very pure; it's slightly damaged by the chemical treatments. But it didn't really matter because if you're going to clone it, the biology selects out the DNA that's just right. So even though maybe only one in a hundred of the joined DNA molecules will be perfectly okay, that will be the one you clone. So it just really made it all possible because now you could make the DNA really quickly.

Hughes

Had Khorana considered the triester method but rejected it because it wasn't as accurate?

Kleid

That's right. They always had a small group not only synthesizing DNA but also developing new methods. They definitely did all the studies on the triester approach, the pros and cons of it, and as far as what Khorana wanted to do, it was not going to be useful.

Hughes

Why did Itakura take that route? Didn't he start working on synthetic DNA before recombinant DNA came along?

Kleid

Right. Like Narang whom I met a few times. He was from Canada and he was making DNA using this triester approach because he wanted to purify the DNA on silica gel. That's very quick, whereas we had to purify it on cellulose, which took a week; the columns took a week or two to run.

Hughes

Because the molecules were so big?

Kleid

They were big and sticky, and the way that this column worked with a gradient, it just took forever.

Hughes

So Narang was trying to speed up the process.

Kleid

He was trying to speed it up. When you use it with the silica gel, you could do the thing in a day, so that was really taking a lot of time off. The reason he could do that was the phosphates were all blocked, so the DNA molecule was acting more like a lipophilic chemical rather than a diester where every single molecule has a charge at a particular pH. You were separating the molecules by charge, so you could really do a nice job in separating them because you could see a two and a three and a four plus charge each come out separately on this column. It took a long time but it was very, very elegant; whereas this triester was not elegant and was not clean, but it was fast.

Hughes

Was speed mainly why Itakura was using the triester approach?

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Kleid

It was. You could actually make the DNA in a reasonable time. As I said, for this one gene, the piece of DNA that I worked on was six months of labor for one piece of DNA.

Hughes

Was it serendipity that Itakura got linked up with Herb Boyer and the recombinant DNA business? I mean, he didn't choose the triester method thinking, "I don't have to worry much about the purity of this approach because I'm going to clone the DNA."

Kleid

Exactly. It is very much serendipity. Art Riggs at City of Hope wanted to make the lac operator and study it chemically, so he linked up with this young graduate student, Keiichi Itakura. Art was very impressed with his ability so he brought him to City of Hope. Dr. Itakura worked at Caltech for a time. Then Riggs got Itakura started at a lab at the City of Hope doing this. Itakura's first student co-worker was Scheller. They worked together at Caltech. They started using the chemistry to make DNA molecules called the triester approach. As I said, there was just very little interest in the whole United States, anywhere, in making DNA; so this was really an outpost.

The methodology that they chose, the triester approach, is what Itakura developed as a student. He thought it worked really well. I think he had more impact on the development of this than his mentor, Dr. Narang. At scientific meetings during this time, Dr. Narang talked about Itakura--and another Japanese scientist who worked with him--and how many hours and hours they would spend in the lab, what terrific scientists they were, and how dedicated they were to making this work.

So Narang and Itakura were perfectly happy with the quality of the DNA from the triester chemistry. Even though it wouldn't satisfy Khorana's group, it would certainly satisfy them. There's no question in my mind, they weren't really thinking about how the triester method would be okay for cloning. It was much faster, and it turned out that it was just the perfect thing. We didn't really need the DNA to be super pure; the bacteria would take care of it.

Courted by Boyer and Swanson

[Interview 2: November 29, 2001] ##

Hughes

Please start by telling me the reason, or maybe the reasons, that you decided to give up a secure job at SRI and start in with this new and unknown company Genentech.

Kleid

As I recall, the start was a phone call from Herb Boyer, who, as we mentioned, Herb Heyneker worked with as a postdoctoral fellow. Herb Heyneker was a good friend of mine over the last five or six years. We're talking about the end of 1977?

Hughes

Probably, because you started at Genentech in '78.

Kleid

So I think it was December of '77 Herb Boyer gave me a call and mentioned that he was talking to Herb Heyneker about the work I was doing and wanted to invite me out to dinner. So I agreed to do that. I went to San Francisco and met with Herb Boyer and Bob Swanson at a

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French restaurant in San Francisco. We had a very lovely dinner. They told me about this Genentech company that they started. At that time the company had no location, and they told me that now they wanted to have an actual facility with employees and everything.

Hughes

Had you met Herb Boyer before?

Kleid

I had been to his lab a number of times. We used to go to seminars at UC Med Center, and I had been in his lab. I may have been introduced to him, but I actually can't recall that now. The first time I really had a conversation with him was at that dinner.

Hughes

How did the conversation go?

Kleid

Well, they described to me that they had started this company, Genentech, and they felt it was time to move into their own facilities. They explained to me what they had been doing at UC and at City of Hope on the insulin project. They said it was time for them to build a place, and they would like me to be part of it. I came to that dinner with the idea that Dave Goeddel and I were interested in making DNA molecules, and maybe we could work with them. We could help synthesize some other genes they might be interested in downstream, so that was my mind set.

Hughes

Meaning that you would stay at SRI?

Kleid

Right. Because I hadn't heard anything about them wanting to start a company with a physical location; I thought that they were supporting research in universities. So it was pretty much a surprise to me that they wanted to actually start a place. They said that Herb Heyneker was going to come. They didn't know where the facilities were going to be at that point, but they wanted to see if I'd be interested or not.

So we talked a lot about their capabilities, because the first thing I was afraid of was, this is a commercial venture to do DNA, and as far as I knew no company had ever before been involved with that sort of thing. But they said that they had contracts with companies that they were going to enter into or just about to enter into--I don't think they were very clear on whether they had entered into them or were going to--and that they had venture capital funding. At any rate, I was very impressed with that because at SRI, as I said, we spent a lot of time trying to get money to support our research. SRI really loved money from companies rather than the government because with companies they could charge a bit more for overhead. But those corporate funds were virtually impossible to get because most companies are very, very tight with their research money and watch over it very carefully, and to give research money to somebody else is something they don't like to do. But here Herb and Bob were saying, "Oh, we're going to get all this money from these companies." So whoa!

Recruitment for the Human Insulin Project

Kleid

So all right, "What is the project about? How far are we on the project?" We had heard that they were doing insulin, and they described to me that Paco Bolivar had been working with Art

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Riggs doing the cloning of synthetic DNA for the insulin B-chain. They said they had made some progress cloning the insulin B-chain but they wanted to finish it right away. The DNA was made, and Bolivar couldn't spend as much time there as they had hoped. He had gone back to Mexico, and so the project was sitting there and they needed somebody to work on it. I had assumed that they were further along than that. So now all of a sudden there was a bit of work there, and Dave Goeddel and I really knew how to do that particular kind of thing. There weren't many other people in the world that had done that kind of work.

Hughes

You mean DNA synthesis?

Kleid

Well, the synthesis was finished, but cloning synthetic DNA.

Hughes

So they wanted you as cloners.

Kleid

They wanted us as cloners. The DNA was made, sitting there, and needed to be hooked up, cloned, sequenced, and then expressed to make the insulin.

Hughes

There was nobody available in Boyer's lab? They were tied up with their own projects?

Kleid

I don't know what the situation was.

Hughes

It could have been more complicated than that.

Kleid

Well, I know the idea of going to start their own company meant they wanted to move the work from inside the lab into a company, and maybe Herb Boyer's postdocs and graduate students didn't want to do that. Or maybe Herb wanted to keep them on his research projects; he didn't want to decimate his lab, and he wanted to find people that were interested in doing something in companies rather than in academia.

Hughes

Boyer was under fire by 1978 because of the blending of the academic and the company business. So another factor may have been wanting to separate the two activities.

Kleid

That could very well be, because it would be quite a switch: the paycheck would come from a company, not grant money given to the university. Also, this project has a subtle difference: in academia you're trying to discover what mother nature knows; you're kind of approaching the truth as mother nature taught it. The goal is to understand completely, but you never actually get there. The closer you get the more questions you find. Its like going up a learning curve that looks like an asymptote. Whereas in a company you have an idea of what you want to do,