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

Early Cloning and Recombinant DNA Technology at Herbert W. Boyer's UCSF Laboratory in the 1970s

Mary C. Betlach, Ph.D

Interview Conducted by
Sally Smith Hughes, Ph.D.
in 1994

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:

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Cataloging Information

Mary C. Betlach (b. 1945)
Scientist

Early Cloning and Recombinant DNA Technology at Herbert W. Boyer's UCSF Laboratory in the 1970s, 2002, v, 79 pp.

Discussion of laboratory facilities, personnel, competition, and working atmosphere at Herbert Boyer's laboratory in the early 1970s; early work to purify restriction enzymes and plasmids and clone DNA; biosafety concerns; plasmid vector development, approval and certification, and conflicts surrounding dissemination to colleagues; perspectives on division between science and industry; opinions on scientists who merit the Nobel Prize; comments on Herbert Boyer, Stanley N. Cohen, Robert Helling, Ernest Jawetz, Art Riggs, William J. Rutter, and others.

> Interviewed in 1994 by Sally Smith Hughes for the Program in the History of Biosciences and Biotechnology, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

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

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

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

Oral histories in process:

Stanley Cohen

Chiron Corporation

Roberto Crea

David Goeddel

Herbert Heyneker

Thomas J. Perkins

Dennis Kleid

Arthur Levinson

G. Kirk Raab

William J. Rutter, vol. 2

Richard Scheller

Keith R. Yamamoto

Daniel Yansura

Interview History

Dr. Betlach was interviewed in 1994 about her position as key technician in Herbert W. Boyer's laboratory at UCSF at the time of the creation and early expansion of recombinant DNA technology. Although the inspiration for the interview came from an oral history conducted that year with Dr. Boyer, her central role in the development of several procedures that made recombinant DNA widely practicable are historically as well as technically important in their own right.

Betlach came to Boyer's lab in 1972, eager to work on restriction enzyme modification, the lab's central focus. It was to become the reason for Boyer's collaboration with Stanley N. Cohen of Stanford in the genesis in 1973-1974 of a straightforward method for combining and amplifying DNA. Betlach describes her participation in the development of recombinant DNA technology and the laboratory's role in disseminating it to molecular biology laboratories worldwide.

Although Cohen's technician at the time, Annie Chang, is co-author of three papers on recombinant DNA published in these years, Betlach, who also played a seminal technical role, is not an author. When the topic came up in the interview, she was characteristically nonchalant. Because as a general rule, technicians are not named as authors of scientific publications, Annie Chang's position on the papers could be regarded as the exception to the rule and Betlach's "omission" the more common situation. Whatever the reason, one hopes that the oral history establishes for the historical record that Betlach was far from a pair of hands in the Boyer laboratory; she created and modified procedures instrumental for the development and expansion of recombinant DNA technology. As she describes in the interview, it was Betlach who created some of the earliest plasmids critical to the application of recombinant DNA and sent them out to investigators around the world. She also reflects on the atmosphere of the laboratory which, like the man at its head, was simultaneously competitive, laid-back, and amazingly productive. Both Betlach and Chang went on to earn doctorates in the biomolecular sciences.

Betlach's view of the accomplishments and culture of the Boyer lab at the height of its preeminence has obvious historical merit. The interview is also a welcome extension of the Boyer oral history and the oral histories in progress with Stanley Cohen and Herbert Heyneker, a postdoctoral fellow in the Boyer laboratory in 1975-1977. Together they provide novel historical documentation of the earliest manifestation of a technology destined to transform biomedical science and to become a major basis for the biotechnology industry.

Sally Smith Hughes, Ph.D.
Historian of Science

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

July 2002

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The Herbert W. Boyer Laboratory at UCSF in the Early 1970s

[Date of Interview: March 25, 1994]## ## This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

Old Facilities in the Microbiology Department

Betlach

We were in an old part of the Medical Sciences building and the labs were pretty funky--old-fashioned histology labs. We didn't have a lot of space. The chairman of the microbiology department, Ernest Jawetz, came to me on more than one occasion and asked for my help in cleaning the place up. Once he--and he made me laugh--appealed to me "as a wife and a mother," couldn't I please do something about this place? And the only reason it was really messy was because we were crowded. When I came it was disorganized and there just wasn't a lot of space. And a couple of the graduate students that Herb had, Joel Hedgpeth in particular, were kind of messy.

So I reorganized the whole place a little bit. As we got more people, of course it just got worse, and what could I say or do? A small, ill-designed space, you can only organize so well. There's just not too much more you can do. We were having to walk across to another building to take our gel pictures. What is here at Parnassus Pharmaceuticals is a paradise compared to what we had--three tiny rooms.

Hughes

Was that typical lab space at UCSF at that time? Or do you think that your lab was particularly deprived?

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Betlach

I don't know. Herb probably knows a lot more about how it was set up.

We were in an old part of the building and there were new labs in the new towers, Health Sciences East and West, which had just been built. I can remember they didn't even have grass in the courtyard yet. But I don't know the politics that were involved in why Herb got old labs and not new labs. But most of the rest of the people in the microbiology department were in the new towers and there were teaching labs and the departmental office in the old building where we were.

We didn't have a lot of interaction with the other people in the department. We had a dishwashing facility in the new building, a room. We had some interaction with people in [J. Michael] Mike Bishop's lab.

Hughes

Because you were doing similar research?

Betlach

Well, it wasn't that similar. They were doing tissue culture and working on viruses, whereas we were working with bacteria. But they were just nicer to us. [laughter] What can I say?

Hughes

Do you know why Dr. Boyer was recruited?

Betlach

That was before my time, so I don't really know. I came in 1972.

Lab Personnel

Hughes

Who was there when you came in 1972?

Betlach

Not very many people--Joel Hedgpeth was just graduating and Ned Mantei whose job I filled. I came to take his position. I came in as a technician. Ned was going back to graduate school with Charles Weissmann. We both had previously worked for Hatch [Harrison] Echols at the University of Wisconsin. Let's see, Bob Helling, Daisy Roulland-Dussoix. That's all that comes to my mind right now.

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Hughes

What was she?

Betlach

It was so long ago and there's been a lot of postdocs and sabbaticals and everything under the bridge since then. I think she was not a postdoc. I think she was higher than that. I think she was on sabbatical or she had some temporary appointment. Herb should know that. Bob Helling was definitely a sabbatical.

So there weren't very many people at first, but then six months after I was there, Pat Greene came in as a postdoc. And then other people started coming, like Paco Bolivar and Ray Rodriguez and Bob Tate and Herb Heyneker, and we started to really get crowded.

Hughes

This was when the research was heating up?

Betlach

The increase in people happened because, yes, we started to--

Studying Enzyme Restriction and Modification Then and Now

Betlach

When I first went there, I was purifying restriction enzymes, of which there were not very many known, and there are hundreds now. Bob Helling was isolating plasmids and running them on tube gels. Pat [Patricia] Greene came and started to set up a gel assay for our restriction enzyme purifications, which previously had been done on sucrose gradients, which was laborious.

Hughes

What does that change in technology mean?

Betlach

That was a big leap. Initially, restriction and modifications systems were investigated in vivo. For example, you could infect an *E. coli* strain with unmodified phage and you'd see if your phage titer decreased in comparison to control strains that either contained the restriction modification system or did not. The presence of the restriction modification system in the strain you were testing was indicated by a decrease in titer since the phage would be susceptible to digestion by the restriction enzyme.

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For purifying restriction enzymes we used an in vitro assay. We took radioactive lambda DNA and we'd mix it in a tube with our enzyme preps that we were assaying. So you'd collect fractions across a given column during any purification step. There would be several different column purification steps and you'd have these fractions and you'd take a small amount and you'd react it with the radioactive lambda DNA and then run it on a sucrose gradient. So each sucrose gradient was one sample, one fraction we were assaying, so it was really labor intensive. The sucrose gradients were run in an ultracentrifuge, fractionated, and counted in a scintillation counter. A lot of work.

Today you take an enzyme sample; you react it in the tube the same way only the DNA is not radioactive--and then you run it in one slot on a slab gel. You can do forty at a time in half an hour, instead of all day to do six because an ultracentrifuge would only hold six samples.

Hughes

Did you have an ultracentrifuge by the mid-seventies?

Betlach

Yes.

Hughes

I know you didn't in the beginning.

Betlach

Yes, we had one and a cold room we used for enzyme purifications. I was trying to remember where our Sorvall was. I can't remember where it was.

Ernest Jawetz and His Lab Group

Betlach

I remember that sometimes we needed an extra Sorvall centrifuge and that across the hall in the department, the chairman had a Sorvall in his lab. But he was an old-fashioned guy, Ernie Jawetz. His Sorvall was absolutely spotless and never used and never touched and he would not let us use it. I got to use it sometimes because he thought that I was neater and cleaner than the rest. It was really sexist. [laughter] The Sorvall was actually under a plastic sheet. Here we were slaving across the hall, people lined up trying to use this other

piece of equipment, hopelessly overloaded. That's the kind of atmosphere; that probably tells a lot.

Hughes

Was there tension between the two labs?

Betlach

Sure. Not only between Herb and Jawetz, but also with the whole lab.

Hughes

You mean one lab against the other?

Betlach

Well, he didn't really have very many people in his lab. All I can remember him doing was walking around in his white lab coat. I'm trying to remember the names of the people involved in setting up the microbiology classes, people pouring agar plates and so on.

Hughes

There was a woman named Hanna.

Betlach

Lavelle Hanna. White hair, yes. And then there was another one with dark hair and glasses. I can't remember her name. I liked her a bit better. They were all sort of remote, that threesome. Not very friendly, and like old-time microbiologists from the '30s or something. Just a different generation.

Hughes

And working on chlamydia, weren't they?

Betlach

I don't even know what they were working on.

Hughes

That says something in itself about the lack of communication.

Betlach

Yes, I didn't even know what he was working on. It didn't seem to me like it was working. [laughter] He was just being the chairman. Low key. We were turned up a couple of notches from them. Some resentment there.

They did do some remodeling on one of the labs and made an office for Herb when I was there. They did do that for him.

Hughes

So the gist is that Dr. Boyer didn't feel particularly supported?

Betlach

I think that's probably true.

Hughes

A classical microbiologist might have recoiled when you mentioned molecular biology.

Betlach

But there really wasn't molecular biology back then.

Hughes

Why do you say that?

Betlach

I think of molecular biology as being more modern, using recombinant DNA technology and cloning and working on the molecular level. We weren't working on the molecular level at first. We were doing restriction modification studies *in vivo ,* which was more similar to what Jawetz was doing. But then we were starting to leap forward, doing *in vitro ,* studies, getting more to the molecular level, see? And Jawetz wasn't doing that.

Hughes

How were you thinking of yourselves?

Betlach

What do you mean?

Hughes

What were you? Were you geneticists?

Betlach

Well, each person in that group had a different background. Bacterial geneticists and biochemists are probably what we thought of ourselves as. We were just doing what we thought was interesting. And you make the leap, and you have an idea, and you test it. As I said to you on the phone, I feel like the work that I've been doing almost at every time of my life has been inherently interesting.

It was really obvious when we started to clone DNA from other organisms--it was the first time that that was being done--that that was a large advancement. We didn't know all that was going to come out of it, but we recognized that it was important. Herb really early on was talking about cloning insulin. And I used to think, that's a little bit far-fetched!

And all kinds of jokes about cloning frog DNA. Are the bacteria going to croak? Are they going to be green? It was fun.

Atmosphere of the Boyer Lab

Hughes

Talk about the atmosphere of the lab. Was there interchange at all levels? Everybody working together and exchanging ideas?

Betlach

Within the lab it was terrific. It was incredible. I was in that lab as a technician. I didn't have a Ph.D. and I was treated as an equal. There was a free flow of ideas. It didn't matter what level you were at. There was just a really good combination of people and there was a lot of free interchange of ideas.

Any idea I had was equal to any idea Herb had or any idea that any postdoc had. It was a real exciting time.

Hughes

Were you working long hours?

Betlach

Yes. And weekends.

Hughes

Weekends, really? That's just what you did?

Betlach

Yes, right! The work was interesting. You'd come in to follow something through because you had an experiment that was in the middle of being done. You didn't even think twice.

I was married at the time and my husband was pretty mad about it. He wanted me to be home at five or six every night. I got divorced soon afterwards. He was sort of jealous that my work was so gratifying to me and that the intellectual atmosphere of the lab was so stimulating to me. It was an extremely interesting place to be.

Hughes

Was it unusual to have such free interchange regardless of who you were?

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Betlach

Not real unusual. I think you could find it in a number of places. I always sought out that kind of environment, and I had had it in other places before I came to Herb's lab. In Jawetz's lab it would be unusual.

Hughes

When you moved to the Department of Biochemistry you found the same free flow?

Betlach

Sure. If it's a good lab, it will be that way. It could be a good lab and not be that way but then I wouldn't want to be in it. When I was at the University of California, Santa Barbara, in Ed Orias's lab, it was also that way, but we weren't breaking ground in quite the same way as we were in Herb's lab. And at Hatch Echols's lab at Wisconsin it was also that way.

Hughes

You felt that you were at the cutting edge?

Betlach

Yes, but I felt that at other times. As I said, I always feel like the work I'm doing is inherently interesting and is on the edge or is interesting to me, and that's enough for me.

Recombinant DNA Technology

Early Development

Betlach

The part where it made a difference was when we could see recombinant DNA technology was going to have these really broad applications. And that added another level of excitement until we started getting negative press. That was kind of bad.

It was exciting to think about what the applications were, the type of things we could do. Everybody was sending us DNA which we were cloning like mad once we finished cloning the *Xenopus* DNA. And so there was just an incredible variety of experiments going on and people contacting us from all over the world.

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Hughes

Follow that through a bit more systematically, perhaps beginning in 1972 when you arrived. The first cloning paper was published in 1973, S.N. Cohen, A.C.Y. Chang, H.W. Boyer, and R.B. Helling, "Construction of Biologically Functional Bacterial Plasmids *In Vitro," Proceedings National Academy of Sciences* 1973, 70: 3240-44. so it appeared pretty close to your arrival.

Betlach

Yes. I came and I started to purify restriction enzymes. Bob Helling was there and he was running plasmids on tube gels. Herb had started this collaboration with Stan Cohen. They put together the idea of restriction enzymes, plasmids, maybe we can do something. Yes, that was a pretty exciting idea. Annie Chang and I both did that experiment. I can't remember if we cut it and they ligated it, but I know for sure that I screened the clones because I had the original DNAs for a long time and I remember doing it, and we had really crude ways of doing it. We had to work out methods for purifying plasmid DNA from these clones in order to characterize them. The technology has since advanced a tremendous amount.

Hughes

So you had to invent that methodology? It wasn't in the literature.

Betlach

Oh, yes. In fact, I still have some of our original procedural write-ups See appendix. , and we kept actively improving them all of the time. When these procedures got out into other people's hands, they developed faster and faster. My feeling was once I got any given method to the point where I could get what I wanted out of it at a reasonable pace, I didn't want to spend any more time working on the methods. I wanted to move on and actually do the work.

I have a procedure handwritten by Herb, "The Betlach/Boyer Plasmid Purification Procedure." It's two-pages long and involves many time-consuming steps, such as using a flash evaporator for one sample. And now it's just a lot more streamlined and you can buy commercial kits to do this. It was just like the Dark Ages what we were doing. It was pretty exciting.

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Authorship of the First Paper

Hughes

Why wasn't your name on the paper?

Betlach

Well, Herb has said a lot of times since then that my name should have been on that paper, and I think it probably should have been because certainly I made at least as equal a contribution as Annie Chang did. I have to say that I am a different person now than I was then, and I didn't think then to speak up to say, "My name should be on this paper." Whereas now, I would. This was unfortunate for me, but I was pretty young and naive.

Hughes

It wouldn't stand out if Annie Chang's name wasn't on the paper.

Betlach

I know. I was just trying to remember how long I had been there. Maybe at that time I was fairly new and Herb couldn't predict how much of a contribution I was going to make and how dedicated I was going to be.

Hughes

Well, that paper had to have been published before June of 1973 when Dr. Boyer talked about cloning DNA at the Gordon Conference [on Nucleic Acids]. The first paper on cloning was published in November 1973.

Betlach

I started in '72, in the fall, so it could very easily be what I said.

Hughes

That you may not have been in the lab for more than just a few months?

Betlach

Yes. But I did do--

Hughes

You did the work.

Betlach

Yes, it also may have been what I said. And as you said, the omission wouldn't be so glaring if Annie Chang also wasn't on there. And also if my contributions since then hadn't been what they were.

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Contemplating Commercial Applications

Hughes

Were the potential commercial applications of what you were doing immediately apparent?

Betlach

Well, Herb kept saying, and I can't put a date on it, "We can probably clone insulin." Or, "This could have benefit for society." So I have to say he was probably thinking that way. I wasn't. I was just enjoying the pure science.

Hughes

But it wasn't clear for some time that you could actually express proteins, was it?

Betlach

Yes, probably not. But I'm telling you, Herb was saying insulin really early. You can ask him and I'd be curious if he could remember exactly when, but I just know he was thinking about that long before anybody else.

Although if you think, okay we can clone human DNA, fly DNA, whatever it is, in bacteria, it is not a big conceptual leap to expression. You would think, maybe we can express it; we can grow a lot of bacteria and they'll be little factories. Although we didn't even know that much about promoters or regulation of expression then!

Cloning Eukaryotic DNA

Hughes

Well, do you want to talk about the frog *[Xenopus laevis]* work? It did cause a stir.

Betlach

Well, yes. I can remember it fairly clearly. I can remember what room I was in when I did it, of all the three labs. In our tenure there, I moved around to various rooms and I can remember that there weren't very many people there yet. And for some reason I can remember what the plates looked like, probably because it was a unique experiment at that time and it was done differently than other experiments. I remember handling the clones and making the DNA. I remember pretty clearly. I guess that says that it was different. Because that was a long time ago.

Hughes

Was there excitement when you saw that it actually did work?

Betlach

Sure! Yes. [laughs]

Reconstructing the Experiments

Hughes

Talk more about the technical parts of it. How did you single out the clones that actually had inserts?

Betlach

What we had to do was make plasmid DNA from the clones-- This reminds me a little bit of those depositions that I've been at when they're asking me to reconstruct experiments. [laughter]

Hughes

Sorry about the bad memories!

Betlach

No, not bad memories. It's just that I've done a lot of experiments since then. I'm just trying to reconstruct and I'm sure there's some gaps, but I can remember we made plasmid DNA. We grew up a liter of each clone. A liter, you know? Now we grow a couple of milliliters. It was horrendous.

Hughes

Why so much?

Betlach

Because there was really no method for doing it and we were trying to work out a procedure. Also, we thought that the DNA could be used as substrate for the restriction enzymes that we were purifying. One of Herb's major interests at the time was in characterizing the *Eco*R1 restriction enzyme, and these plasmids could be used as a substrate for the enzyme. But gee whiz, one liter and you have enough DNA forever. [laughter]

Actually that became apparent to me sooner than it did to Herb. Because I remember grumbling and thinking, we should grow up less. He kept insisting, "We can use this as

substrate for the enzyme." So I was already thinking, before him, that this procedure has got to be scaled down because it was in my hands and it was really horrendous.

Now what else was I talking about? Making the DNA. You purify the DNA and then it would have to be run on the gel and stained. We were doing these polyacyrlamide tube gels and they'd have to be stained.

Hughes

Why tube gels?

Betlach

Now, Bob Helling was the one that set that up in our lab. And he was doing it to characterize the plasmids found in different bacterial strains, and I think he published some papers on that work. I'm just trying to remember how that apparatus developed. Maybe tube gels were developed for some other purpose and he adapted them.

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Betlach

I remember when Pat Greene came, she established an agarose method in our lab. We were trying to figure out at first how to take photographs of these gels. Now companies sell special equipment for this. We were going down to the UCSF photography department and trying different filters and lights so we could get good pictures and documentation of the gels. We were having to work all of that out every step of the way. But that's the way science is. Now, it just seems like the Dark Ages because these things have evolved so far. Most of the time I don't think anything about it, but other times I just feel like some old fossil. I was one of or the first cloner. And here I am still doing it.

Hughes

What kind of reaction did you get from the scientific community?

Betlach

At what stage?

Hughes

Well, the way I read it, and I would like your opinion, is that DNA cloning wasn't making too much impression on the science community until the Gordon Conference.

Betlach

When exactly was that? I didn't go to the Gordon Conference.

Hughes

That was June of 1973. Dr. Boyer had an agreement with Dr. Cohen that Dr. Boyer would not say anything until the paper was published, which was in November 1973. In the enthusiasm of the moment, or whatever--I don't know what his motivations were--he did talk about it. It fell flat until somebody at the Gordon Conference picked it up and then the implications became clear. A result was the Singer-Söll letter.

Reporting the Discovery

Hughes

Do you remember talk about keeping the research quiet until it was published?

Betlach

No, I can't remember about that specific instance, but I can probably shed some light on why it might have happened like that and on Herb's personality, which might help you. I don't like my postdocs to talk about work unless it's actually been submitted for publication. If it's submitted, it's okay. It's better if it's accepted, but at least if it's submitted, if they're going to reject it, at least we've got something that we can rework and send back. But some labs have policies that you're not supposed to talk about work until it's published. So it sounds like there was a difference in opinion between Herb and Stan Cohen.

Herb is the kind of guy that never held anything back. He's not as uptight as I am about that. As soon as something happens, he doesn't care if it's written up, he wants to talk about it. This can be a disaster, but on the other hand it really helps the flow of scientific ideas. Also, Herb was not really good about getting things written up. [laughs] Stuff would end up being written up in weird places, proceedings of meetings and stuff like that. I realized, he would rather do his science and not the writing.

Hughes

Once he wrote it up, he didn't necessarily put it in the best journal?

Betlach

No. He didn't really care. Some of our stuff was published in the weirdest, funkiest places. Some of the stuff should have gone to really premiere journals, and didn't. Now, years later, if I publish work in meetings proceedings, it's usually review-like in nature and

contains little really new data. I don't think it's that Herb didn't feel confident in the work; I think it's just that he didn't like to write that much.

Hughes

Well, the 1973 paper was published in the *Proceedings of the National Academy of Sciences.*

Betlach

Well, that's good.

Hughes

Why would they have chosen that journal?

Betlach

That's a good journal and it has a really wide readership and it's an appropriate place. So that indicates they knew it was important--Stan Cohen, I'd say. I just feel Herb doesn't control his contributions into the literature that much. He likes to got to meetings and talk about it and tell people about it. He likes to do the science. I bet that was Stan Cohen's decision. But don't tell Herb I said that. [laughs]

Hughes

Are there differences in scientific styles between the two men?

Betlach

Yes. Stan Cohen is a little more tense and controlling. We had Herb's retirement party a couple of years ago, and Stan came to it and it was really nice. A lot of people came to it. It was really fun.

Hughes

They don't see each other very much now?

Betlach

No.

Hughes

Did the collaboration end after the cloning work?

Betlach

Not much happened after that. Maybe some minor things, but nothing that I can remember specifically.

Biosafety Concerns

Hughes

Relating to the recombinant DNA debate is a paper by Dr. Cohen stating that transfer of DNA occurs under natural circumstances. This was supposed to allay the fear of breaching species barriers and the potential hazard of recombinant DNA research.

Betlach

Yes, and that transfer does occur.

Hughes

Was it a big deal that he showed experimentally that it could happen?

Betlach

I can't exactly place that piece of work to this time. But we were not worried at all at first, and then it became clear that maybe there might be a reason to worry.

Hughes

When and why?

Betlach

There was the meeting at Asilomar [February 1975]. I remember, I was doing a lot of cloning of DNA from all kinds of organisms. [laughs] It was like the zoo. We just put them on the shelf; we just quit; we just stopped. I can't tell you exactly when.

Hughes

You're not sure that it was after Asilomar?

Betlach

I think, if anything, it might have been before. As soon as there was any clue at all, before that meeting. But I just can't recall exactly. I'd have to look through my old notebooks, which I no longer have. Three years of my notebooks disappeared at some point.

Hughes

Really.

Betlach

And I am very careful about my notebooks. I gave a lot of them to Herb when I left UC. In some of the patent contests that have been going on between Lilly and Genentech and UC, I was deposed a couple of times. The last one I was up for, they asked me, "Do you know what happened to your notebooks between the years 1976 and 1979?" I think those

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were the years. And they're just gone. There was an earlier stage when I was giving testimony when they were there, and large chunks of them were copied by various people involved.

Hughes

But you got them back?

Betlach

I got them back after parts of them were copied, and then they subsequently disappeared. I never lose anything like that. I have every single notebook I ever had, except for those that were lost and the ones I gave to Herb.

You asked if we were aware of the possible dangers.

Hughes

Yes. Can you recreate the feeling of that time?

Betlach

Were we really worried, you mean?

Hughes

Yes, and how did you react to the dissenting scientists and the environmental groups that were activated on this subject.

Betlach

Well, I can only speak for myself. I felt that there probably wasn't any danger, but I didn't know, okay? Especially human clones, you just really didn't know. So we put them on the shelf. Probably it would have been better to autoclave them.

When we got so that we had to certify vectors and things, we went through some really tedious testing, putting them in crippled bacterial strains, to make sure that there wouldn't be any danger. And if you sat and thought for a couple of minutes: these genes are in bacteria. Are you going to inhale them? Or maybe you're going to get them in your gut. Your body's going to have defenses against these kinds of things and probably nothing is going to happen.

We were aware that there might be mechanisms that we didn't know anything about, so we were as careful as we could be. And I think it was overkill. Even then I was thinking what we had to do and all of this furor about P3 [physical containment lab level 3]. I was

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far more afraid of working with hepatitis virus or Rous sarcoma virus, like Mike Bishop was working with at the time. Tissues from diseased patients, I think, were much more dangerous.

Hughes

So you weren't particularly afraid for yourself?

Betlach

No, I wasn't worried. But I was young and did all kinds of things in those days, like not using gloves when using ethidium bromide and using huge amounts of P32 [radioactive phosphorus]. Now I wouldn't do such things.

Hughes

It wasn't an awareness in that era?

Betlach

I wasn't the only person. [laughs]

Hughes

It was standard behavior, is what I'm asking; it wasn't that you were a risk-taking person?

Betlach

No. Ethidium bromide, I just didn't know; I thought it was okay. When I learned otherwise I started wearing gloves. Radioactivity I should have probably known better and times change and people use less radioactivity in experiments now. But these clones--I didn't think there was any danger. But I didn't know for sure. I remember clearly having this feeling, especially with human DNA: there may be some mechanisms I don't know. Okay, we'll just put these away, and we've got plenty of other things to work on. And we did. That's my personal feeling.

Hughes

Do you know for what period they were put on the shelf?

Betlach

Oh, for a long time. We completely shelved a whole bunch of experiments. We had been sent DNA from people to do experiments with. When specific experiments with human DNA, for example, started up again, they were P3, and each experiment was usually assigned to one postdoc. It wouldn't be just me slinging hash on six things at once. I was much more focused on making vectors by that stage. By then we'd send vectors out and the recipients would be doing the cloning experiments themselves in their own labs.

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And then we had a couple of projects where Herb thought that he was going to get interested in immunology. I remember him saying, "Immunoglobulins are going to take up the next twenty years of my life." We had a couple of postdocs who were starting to work on that, and so I just didn't work on any of those experiments anymore. I started to make vectors and improve vectors, which was kind of fun.

Hughes

When you were thinking about risk, what exactly were you thinking might happen?

Betlach

I didn't know. I was a bacterial geneticist. At that time I didn't know anything at all about eukaryotic systems, except in very gross terms. In fact, not that much was known at the molecular level on human systems. Period. However, I was afraid of Rous sarcoma virus and hepatitis virus. I just thought, I don't know about this, and there may be mechanisms that we don't know about and it's just not worth it. I wasn't terrified by it. I recognized that we didn't really know all that was going on. Actually, if there wasn't a lot of fuss about stopping it, I probably would have just done it, but it would have made me a little uneasy.

Hughes

Presumably you started again when the NIH recombinant DNA guidelines were weakened and such experiments were now permissible.

Betlach

Yes, but that's the period when I said that I was focusing on something else besides cloning the DNA everybody was sending. Individual postdocs had projects where they would work with one sample of DNA. At the early stage, before the Asilomar meeting, we were the only place that was doing it. So people were sending us DNA, and we were cloning all kinds of things. Later, we started to focus on interesting new projects that would use this tool.

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Plasmid Vectors

Plasmid Development in the Boyer Lab

Hughes

Well, talk about vector development.

Betlach

Sure. Now let me shift gears. Of course, we wanted to develop vectors that would be widely useful. I know that's what Paco Bolivar and Ray Rodriguez wanted to do. My feeling was, I want to make a vector I can use to do things I'm interested in. I don't want to make vectors for the rest of the world.

Hughes

They were in the Boyer lab to make vectors rather than to pursue their own research interests?

Betlach

Many people who joined the lab at this time came to learn the new technology. I don't know the specifics reasons they came for. When they arrived I was already developing new vectors, and then they took ones I had made and refined them more.

Hughes

Go into exactly how one does that. Do you want to use pMB9 as an example?

Betlach

What they wanted to do was to make the plasmid easier to use, so it would have more general utility. Put more antibiotic resistance markers on it, so that you could clone in one antibiotic-resistant gene and inactivate it and select for the other marker. We could already do that with pMB9, which has the markers tetracycline resistance and colicin immunity. However, colicin immunity is a tricky marker to use.

They wanted to use ampicillin resistance and then the idea was you would clone in, for example, the tet gene and your transformants would be still ampicillin resistant. But they'd be tet sensitive and then you'd have a way to tell which clones were which without looking at the DNA. So it's actually a screen. And they wanted to make the plasmid smaller, take it down to the basic elements so you have less DNA there, and make maps of it so you know all the sites in it. Then Greg Sutcliff sequenced the entire thing, pBR322.

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Hughes

What about sequencing techniques at that time?

Betlach

Primitive, primitive! John Shine was doing some and Joel Hedgpeth did some too. It was primitive and very difficult compared to now, just like everything else we were doing then.

But the way we got started on doing vectors was we had originally pSC101 which came from Stan [Stanley N.] Cohen's lab that was tet resistant and did not have very many copies per cell, so you didn't get a lot of DNA. It was big and difficult to use.

Meanwhile, the problem I was interested in was, I wanted to clone the *Eco*R1 endonuclease genes onto a multi-copy plasmid. Hopefully then it would be expressed at higher levels. We'd have an over-expressing strain so when we made restriction enzymes we'd get a lot more enzyme. I tried to isolate and clone the *Eco*R1 endonuclease and methylase genes, and it turns out, they were already on a multi-copy plasmid. Actually, that's an interesting story, too.

Isolation of *Eco*R1 and the Development of Betlach Plasmids

Betlach

*Eco*R1 was originally isolated from a clinical isolate from the UC labs. You can ask Herb about this. It was isolated from someone's urinary tract infection. [laughs] Multiple-drug resistant *E. coli* organism. A student of Herb's named Bob Yoshimori got that strain and worked on it first a little, and then left.

So I took that strain and was trying to clone these genes from it. I characterized it and we found, as I said, that the R1 genes were already on this multi-copy plasmid. And then I cloned the methylase gene. That was probably the second cloning experiment done anywhere. This plasmid, it turns out, was multi-copy, and then we also had pSC101, this large low copy number plasmid from Stan Cohen which was difficult to use but that had tet resistance on it.

The first plasmid that I isolated from the clinical isolate I named pMB1. It was big too, but it was multi-copy, so we tried to get it down a little bit in size. We didn't have very

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many restriction enzymes at that time, so I took pSC101 and pMB1 and did an *Eco*R1 star digest which is a decreased specificity for the *Eco*R1 site. This probably all means nothing to you. It was like a witch's brew, okay? We didn't have a lot of tools to work with and I just sort of mixed things together, selected for tet resistance, and hoped for the best. Out came a bunch of clones, one of which I named pMB9, that contained the tet gene from pSC101, but the origin of replication from the multi-copy plasmid, pMB1.

Hughes

Do you do the procedure very deliberately so that you know that you're going to get the tet gene?

Betlach

Not exactly. I selected for tet resistance, but a fairly random mixture of fragments was used. There were not very many restriction enzymes and no restriction maps yet. There was *Hind*3 and there was *Eco*R1. If you react *Eco*R1 under certain conditions, you get a decreased specificity, so it hits in more places. But it's almost random, so I digested a mixture of pSC101 and pMB1 with this fairly random-cutting enzyme. I put a selection on for tetracycline resistance. I selected for that so it would pull a little fragment containing tet resistance out of the mixture. I always felt like it was a witch's brew, and I guess I was the witch. [laughter]

I remember I got this set of clones and I ran them out on a gel and there was only one that looked any good. I thought, oh, I can't wait to check that one out, and I went on vacation for a month because it was in the middle of the summer and I had already made these vacation plans and I couldn't find out the result until I got back. I came back and then I characterized it and the one promising clone (which I named pMB9) was good for a lot of things. I could do a lot of things with it and so that's why I stopped developing it. It was small, it was multi-copy, it had tetracycline resistance on it. It was useful. And we gave pMB9 out to a lot of people.

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Plasmid Dissemination

Hughes

What is the protocol in science for exchange of materials?

Betlach

Well, usually once you publish information on a strain or plasmid etc., you're morally obliged to give it out. Before publication, you're really not. In fact, some journals stipulate that you have to give out anything that's published in their journal. Not everybody does, but we freely gave out all sorts of materials. We gave out pMB9 all over the world before anything was published on it. It didn't bother me. I didn't care because I wanted it to use it for experiments and it was fine. And if it's useful for other people's purposes that aren't in competition with you, then why should it bother you? So we gave it out all over the place.

Hughes

Were there any restrictions?

Betlach

None that I can remember.

Hughes

Did you stop distribution for a while when there began to be the concern about recombinant DNA?

Betlach

Well, we had pMB9, pBR313, and pBR322, and they were being tested. I think we did stop sending them out until we got the plasmids certified. Or I may have given them out to some people, but told them that we were waiting for certification and they couldn't use them before we got it. I can't remember exactly, but I think it makes sense that we just stopped sending it out.

Hughes

That leads into the pBR322 episode. My main source is Stephen Hall's book, *Invisible Frontiers.*

Betlach

That one is pretty good. Accurate.

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Hughes

Yes. *The Race to Synthesize a Human Gene* is the subheading. He maintains that Dr. Boyer in January of 1977 was very clear on the distinction between an "approval" and "certification." Stephen S. Hall, *Invisible Frontiers: The Race to Synthesize a Human Gene ,* (Redmond, WA: Tempus Books, 1987), pp. 116-17. Remember that two-step process?

Betlach

I remember it. It's very clear in my mind.

Hughes

It apparently was not clear to other people in the department.

Betlach

That may have been the case.

Hughes

Namely, to Howard Goodman and William Rutter.

Betlach

Well, I don't know if they were clear on it or not, but I definitely knew that it was a two-step process. People were calling me up all the time. I remember Herb was down in Miami or someplace at a meeting, and the plasmid was at NIH and they were deciding it had been approved and not certified, or certified and not approved, now I'm temporarily confused.

Hughes

"Approved" comes first. Certification was by [Donald] Fredrickson, the NIH director.

Betlach

What's the name of the other guy, Gartland?

Hughes

William Gartland. He was head of the NIH Recombinant DNA Advisory Committee.

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The Boyer Lab Moves to the Biochemistry Department

Hughes

What difference did you find between the Department of Microbiology and the Department of Biochemistry when you moved at the end of 1976?

Betlach

When we moved up to the fifteenth floor in the Health Sciences Towers?

Hughes

Right.

Betlach

Well, we had a giant new lab, and that was great, but we were up on the fifteenth floor and we were fairly isolated at first. For me it wasn't really that much different because we interacted just as much with people in the Biochemistry Department [ninth floor] when we were in the Microbiology Department. There was actually quite a bit of cross-talk between Microbiology and Biochemistry. The departments overlap a lot now. They have the PIBS program--Program in Biological Sciences; the graduate programs are shared in a lot of ways. But it was nice to be away from that oppressive Microbiology Department feeling. But otherwise I'd say the interaction with Biochemistry stayed the same. And we had these gorgeous labs.

Hughes

You didn't have more collegial support?

Betlach

We already had a lot of collegial support from the Biochem department. So, I think it was the same. [William J.] Rutter did an incredible job of building up that department. And there's been a lot of excitement and development into other scientific areas since then. The UCSF Biochemistry Department is ranked first or second in the nation.

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Use of an Uncertified Plasmid, 1977

Hughes

Well, we were talking about the pBR322 episode. You said you were very clear on the distinction between "approval" and "certification."

Betlach

Yes, I knew that we needed both. People would call me up. A lot of times I'd be busy and they'd ask me if pBR322 was okay to use, and I'd say, "It's approved, it's approved!" Not necessarily would they hear that you need both "approved and certified." So you could see people might take my answer the wrong way.

Hughes

All of this was verbal at this stage?

Betlach

Yes, phone calls.

Hughes

What about the insulin clones?

Betlach

All I know is hearsay. I know that people were calling me up and I told them what I told them. Everybody had the plasmids because we were so freely giving everything out. You're asking me whether or not the plasmid was used ahead of NIH certification?

Hughes

Yes.

Betlach

I can give you an opinion. People could have misunderstood what I told them on the phone and could have used pBR322 before it was certified. One could imagine a lot of scenarios. And then, like you, everyone is saying this, that, and the next thing. All I can tell you is my personal feeling and I don't really have anything to substantiate it: Probably pBR322 was used and probably used by mistake because there was a misunderstanding.

Hughes

And then destroyed? Once it was revealed that the plasmid had been used before certification, Axel Ullrich supposedly destroyed the clones.

Betlach

Yes, but the problem with that was the experiment had to be redone.

Hughes

Some people didn't believe that the experiment could be repeated and submitted to *Science* within three weeks. They questioned whether the original clones had been destroyed.

Betlach

The experiments were pretty quick to do and Axel would have all the materials to do it. He'd have the RNA. This is a guy that worked night and day.

It was really sort of an incestuous situation at the time. All of the postdocs in the department were socializing. So you were living with these people all the time, and there'd be big parties, and we partied pretty heavily. All of this was going on. I knew Axel pretty well. He was dating my roommate at the time. My marriage had broken up and I was sharing an apartment with another divorced woman.

I remember when this other woman and Axel and I watched this *Nova* show on TV, recreating all of this. We just sat there, silent. [laughter] It was really-

Hughes

Tense?

Betlach

Not tense. Just quiet, thoughtful.

Hughes

Was the program accurate?

Betlach

I can't remember how accurate it was. I just know we each knew our own truths, if you know what I mean.

Hughes

You didn't ask, "Axel, did you destroy the clones?"

Betlach

No, I did not because by that time I think Bill Rutter had been sending around little notices to everyone saying, "What do you know about this?" Because he was trying to figure out what went on, maybe before going to the Senate hearing. I didn't reply because I felt I really didn't know anything, except hearsay and the fact that when people called me I told them X, Y, and Z. So I wasn't going to contribute to the general paranoia and weirdness that was going around, so I never talked to Bill Rutter about it.

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Hughes

Well, I saw Dr. Ullrich at the Rutter symposium, and I asked him if he would talk with me. An interview with Dr. Ullrich was conducted on April 5, 1994 and will be available after a second interview is recorded.

Betlach

His future wife Suzanne also socialized with us.

Hughes

What lab was she in?

Betlach

She was a graduate student. Subsequently, she got a faculty position at Stanford. [MB] Whose lab was she in? Reg[is] Kelly's? And now Axel's at the Max Planck Institute in Munich. I was there at a meeting last spring and I stopped by his lab, but he was in Spain. I just left him a little note. I haven't seen him in a long time. And the little note I left said, "Here's a blast from your past." [laughter]

Rivalries

Hughes

There was quite a bit of intra-departmental rivalry at that time, for instance, between Goodman's group and Rutter's group. There was also Harvard.

Betlach

Oh, yes, Harvard. I remember we felt the competition with Wally [Walter] Gilbert's group at Harvard. They put out these little newsletters "The Midnight Hustler, See Appendix H." talking like we were sports teams or something. Those competitions were all very good-natured.

Hughes

Even within the department?

Betlach

Well, Herb and Howard had a falling out. We never had any problem with Bill Rutter, and I have a very high opinion of him. Any problems there were between him and Howard, I don't know much about. But I know Herb had a falling out with Howard. We had a lot of interaction with everybody in Howard's lab, up to a certain point in time. In fact it was almost like the two labs were one lab. We had joint seminars and we shared supplies. There was a lot of camaraderie.

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UC's Contract with Genentech on Somatostatin

Hughes

Did you have any part in the work on somatostatin?

Betlach

I had a more peripheral role in somatostatin. At this time Herb had been talking to Bob [Robert A.] Swanson. Genentech had been formed and they wanted to start doing some work. Somatostatin was one thing they wanted to start working on and a contract was set up somehow--all kosher with the university. There was a little bit of money that was made available to the lab to do this.

Hughes

From Genentech?

Betlach

Yes. And so, I was put on it at first, along with Art Riggs. He came up from southern California. Art Riggs didn't know much molecular biology at the time, and so I had to teach him. We were doing the somatostatin research together. He sort of drove me nuts.

Hughes

Why?

Betlach

Well, he's one of these real methodical guys. He's too slow. I was very impatient with him, and I'm not very good at teaching, either. So we started to work on it for a while and then I got off the project. Actually, I remember it fairly clearly because I was deposed for this pretty recently and they went through all the experiments. "Do you remember you did this experiment, etc.?" but that's about all there is to it that would probably be of interest to you. My role was more peripheral.

Hughes

Congress at the time was debating whether legislation should be passed to regulate recombinant DNA research. Which, of course, the scientists--

Betlach

Did not want.

Hughes

The cloning of somatostatin was announced in a Senate subcommittee hearing. The point was to show the commercial and medical possibilities of this technology and allay some of the scare talk. Do you remember--?

Betlach

No, I don't remember much about that. All I know is Rutter was collecting data points from people before he went to the Senate hearing. I was talking to Herb every day, and he didn't discuss with me any strategy about what he was going to say or what they were going to do.

Hughes

Did you get the feeling that they were preparing for the hearing?

Betlach

Just Rutter.

Hughes

But not Dr. Boyer?

Betlach

I didn't have any feeling that he was. But I don't know. Herb has this laid-back style, so he may be preparing for something and you don't have a clue. [laughter] That's the way he is.

Boyer as a Lab Director

Hughes

How true is that laid-back style?

Betlach

It's true, but he's wonderful to work with because he's really intuitive. When he was interested in science it was wonderful to have him around because he's really intuitive and he allows people working under him to have an incredible amount of independence and encourages it. And he encourages you to be intuitive, too! So there's these wonderful ideas bouncing back and forth. But he's very laid back. He's not going to come and tell you how to do things. I've heard it said about him that he gives you enough rope, just don't hang yourself with it. I functioned really well in that environment because I never could stand somebody breathing down my neck. Stan Cohen seemed a little bit more like that. However, with Herb it was take the ball and run.

Hughes

How did his laid-back style work with graduate students?

Betlach

It depended upon the graduate student. Actually, he didn't have that many graduate students. Postdocs did better--they are more independent. Postdocs thrive in that kind of

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environment, but for graduate students it's a little tough. Usually they floundered, unless they were taken under a postdoc's wing.

Hughes

Dr. Boyer told me he didn't like teaching medical students.

Betlach

Yes, he didn't like giving formal lectures to medical students, but he was really good at teaching postdocs in this indirect way because he encourages independence.

Tension over University Ties with Genentech

Hughes

One more question as I know I'm taking a lot of your time: Talk about the controversy that grew up in the early days of Genentech when it was functioning in the biochemistry department.

Betlach

Bad feelings. There were a lot of people in the department looking down their noses at Herb, saying that science and industry should be separate. He was blacklisted by a lot of people in the department, to be perfectly frank. Finally, I think, they've come around and they're all involved in new companies now. But it was pretty bad and pretty crummy treatment of him. I thought Genentech was a pipe dream, to tell you the truth. I thought it wouldn't go anywhere. But it seemed to me, if Herb followed all of the rules that he had a right to try something like that. If he was fulfilling his obligations at the university, nobody had the right to any say about it. That's what I thought.

Hughes

And he was fulfilling these obligations?

Betlach

And he was. It was really irritating to me that these people had this attitude. I continued to be irritated about it for the next twenty years after that. Some of them stayed that way for a long time.

Hughes

How was it expressed?

Betlach

A lot of it indirectly.

Hughes

Was Dr. Boyer cut out of scientific interchange?

Betlach

No, people that were interested in the same things that we were would still interact with us. No, it was more people that were working in other areas of research. All I can remember is disapproving looks, and I don't know specifically what things were done or said to Herb. I do know some, I'm sure, but I can't come up with any specific instances right now that can properly convey the feeling that there was.

Hughes

How did he react?

Betlach

Well, it wasn't fair. I remember I was hurt. I'm not exactly sure if he didn't give a damn or if it bothered him. Some of the people he really didn't think that much of, anyway. So if they were going to have that opinion, it was their problem. But then maybe there were certain individuals who felt that way, and maybe it bothered him, so probably it was dependent upon the individual.

Hughes

Does he talk about it?

Betlach

No, he doesn't. I've known him for a long time and I feel like I know him pretty well. He's laid back, but he keeps a lot of things inside. I don't think very many people know him very well, and I feel like I'm probably one of the people who knows him the best, and I don't know him very well.

Every year when Nobel Prize time comes around, I feel upset for him. I think now he's gotten over a lot of this because he's doing so many different things in his life now. About three months ago I finally sat down and told him how I felt, that I felt like it wasn't right, that I felt like he should have the Nobel Prize. A lot of these things had been unsaid and I just said them.

Hughes

How did he react?

Betlach

I think he appreciated the support, but he wasn't forthcoming. I could see how he felt from his body language and knowing him, rather than by what he was saying. It's easy to scratch

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the surface with him but hard to go deep. So I can see how it would be easy to interview him but difficult to get some things out of him. Kary Mullis got the prize for PCR [polymerase chain reaction]. Herb Boyer should have the Nobel Prize. I think Paul Berg deserved the Nobel Prize; I don't know if it should have been for recombinant DNA. I think for recombinant DNA and cloning, Herb deserves the Nobel Prize.

Hughes

Is there anything more you want to say?

Betlach

I think I've said a lot. I don't know what else to say, except I'm glad I was there. It was fun.

Transcribed by Michael J. McArdle

Final Typed by Julie Allen and Kathy Zvanovec-Higbee

Appendix

Tape Guide--Mary C. Betlach

Date of Interview: March 24, 1994

Date of Interview: March 24, 1994

- Tape 1, Side A *
- Tape 1, Side B *
- Tape 2, Side A *
- Tape 2, Side B unrecorded

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CV: Sally Smith Hughes

Graduated from the University of California, Berkeley, in 1963 with an A.B. degree in zoology, and from the University of California, San Francisco, in 1966 with an M.A. degree in anatomy. After completing a dissertation on the history of the concept of the virus, she received a Ph.D. degree in the history of medicine from the Royal Postgraduate Medical School, University of London, in 1972.

Postgraduate Research Histologist, the Cardiovascular Research Institute, University of California, San Francisco, 1966-1969; medical historian conducting the NEH-supported History of Medical Physics Project for the History of Science and Technology Program, The Bancroft Library, 1978-1980.

Presently Assistant Research Historian in the Department of History of Health Sciences, University of California, San Francisco, and an interviewer on medical and scientific topics for the Regional Oral History Office. The author of *The Virus: A History of the Concept*, she is currently interviewing in the fields of health maintenance organizations, virology, public health, ophthalmology, and molecular biology/biotechnology.
