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

UCSF Oral History Program
Dept. of Anthropology, History & Social Medicine
University of California, San Francisco

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

Herbert W. Boyer, Ph.D.

# RECOMBINANT DNA RESEARCH AT UCSF AND COMMERCIAL APPLICATION AT GENENTECH

With an Introduction by
J. Michael Bishop, M.D.

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

Nancy Rockafellar, Ph.D., Editor
Kathleen Zvanovec-Higbee, B.A., Editor

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:

Herbert W. Boyer, "Recombinant DNA Research at UCSF and Commercial Application at Genentech," an oral history conducted in 1994 by Sally Smith Hughes, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2001.

Copy no. 1

Herbert W. Boyer, 1990s.

*photo credit: Eliot Holtzman*

Cataloguing information

BOYER, Herbert W. (b. 1936) Biochemistry professor/industrialist

*Recombinant DNA Science at UCSF and Its Commercialization at Genentech*, 2001, xvi, 188 pp.

Pennnsylvania family background; education at St. Vincent College, University of Pittsburgh; postdoctoral research on restriction enzymes, Yale, 1963-1966; assistant professor to professor, University of California, San Francisco, 1966-1991; recombinant DNA research: collaboration with Stanley N. Cohen, biohazards controversy, development/diffusion of recombinant DNA, NIH research guidelines, UCSF politics/biosafety policy; Genentech, Inc.: founding, financing, staffing the company with Robert Swanson; the somatostatin, insulin, and growth hormone projects; university relations/reactions; Boyer-Cohen recombinant DNA patents; comments on scientific approach, Gordon Tomkins, writing/publishing papers, self-assessment.

Introduction by J. Michael Bishop, M.D., Chancellor & Professor of Microbiology/Immunology, University of California, San Francisco.

Interviewed in 1994 by Sally Smith Hughes, Ph.D., Department of the History of Health Sciences, UCSF and the Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

TABLE OF CONTENTS--Herbert W. Boyer


BIOTECHNOLOGY SERIES HISTORY by Sally Smith Hughes i

BIOTECHNOLOGY SERIES LIST vi

INTRODUCTION by J. Michael Bishop, M.D. vii

INTERVIEW HISTORY by Sally Smith Hughes xii

CURRICULUM VITAE xv

I EDUCATION 1
St. Vincent's College, Latrobe, Pennsylvania 1
Graduate Student, University of Pittsburgh, 1958-1963 1
Interest in Microbial Genetics 1
The Genetic Code 3
Mentors and Colleagues 4
The Department of Microbiology at Pittsburgh 5
Postdoctoral Fellow at Yale University, 1963-1966 7
Interest in Bacterial Plasmids 7
Postdoctoral Work on Gene Mapping of *E. coli* Strains 8
Evidence of DNA Restriction and Modification 11
DNA Recombination Research at Yale 13

II UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, 1966-1991 16
Faculty Member, Department of Microbiology, 1966-1975 16
Deciding to Come to San Francisco 16
Teaching Medical Students 17
First Impressions of UCSF 19
Colleagues in the Department of Microbiology 20
The Department of Biochemistry 22
William Rutter and Gordon Tomkins 22
Boyer's Associations with the Department of Biochemistry 24
The Division of Genetics 25
Boyer Joins the Department of Biochemistry, 1975 26
Collegiality in Biochemistry 28
Recombinant DNA Research 30
Splicing Plasmids, 1972-1973 30
Stanley N. Cohen and the Plasmid Meeting in Hawaii, 1972 31
Research Prior to the Boyer-Cohen Collaboration 32
Technical Breakthrough: Characterizing DNA Fragments 34
Boyer and Cohen Collaborate on Prokaryotic and Eukaryotic DNA Experiments 36
The Biohazards Problem 37
Cloning Successes 39
Considering Commercial Applications 41
The Research Moratorium 43
The Singer-Soll and Berg Letters 43
Thoughts on Potential Biohazards 44

The Asilomar Conference on Recombinant DNA Molecules, February 1975 45
Diffusion and Development of Recombinant DNA Technology 46
Research on *Halobacterium halobium* 49
Distributing Plasmids 50
Revisiting the Biohazard Issue 50
NIH Guidelines for Recombinant DNA Research 50
Opponents of Recombinant Research 51
The Role of the American Society of Microbiology 52
Concerns for Safe Technique 53
Potential Cloning Experiments 55
Blunt-end Ligation 56
Collaboration with John Rosenberg on Protein-DNA Interactions 57
Nucleic Acid Sequencing 59
The *Smithsonian* Magazine Article and the NIH Guidelines 60
The pBR322 Episode 62
Use of an Approved but Uncertified Plasmid 62
The Senate Hearings, November 1977 63
Announcing the Cloning of the First Human Gene 65
The UCSF Biosafety Committee 66
Risk/Benefit Analysis 69
P-3 Facilities at UCSF 69
The Q Fever Scare 70

III GENENTECH, INC. AND THE COMMERCIALIZATION OF RECOMBINANT DNA TECHNOLOGY 71
Formation in 1976 71
Chemical Synthesis of DNA 73
Somatostatin: Demonstrating the Technology 75
Expanding to South San Francisco, Recruiting Scientists 77
Human Insulin 78
The Race for the Gene 78
Joint Ventures with Eli Lilly and KabiGen 79
Genentech's Primacy in Biotechnology 81
Somatostatin Studies 83
More on Early Recombinant Research at Stanford and UCSF 84
Genentech's Early Goals and Philosophy 87
More on the Joint Ventures with Lilly and KabiGen 88
Boyer's Decision Not to Participate in Genentech Research 89
Promoting and Recruiting for Genentech 90
Comparing Industrial and Academic Science 92
More on Early Corporate Goals 93
Development and Scaling Up 94
Repercussions on the UCSF Campus 96
Issues Arising from Faculty Relationships with Industry 99
Boyer Speaks Out at the Gordon Conference, June 1973 102
Publicizing Scientific Results Before Publication 103
Details of the Cohen-Boyer Collaboration 105
Authorship 105
Recombinant Experiments with Eukaryotic DNA 107
DNA Fragment Closure Rates 110
The Species Barrier 111

Preparing Purified Plasmid DNA 111
Diffusion of Recombinant DNA Technology 112
Effect of the NIH Guidelines 113
Commercializing Reagents 114
The Boyer-Cohen Patents 115
The Process Patent, December 1980 115
The First Product Patent, August 1984 118

IV SUMMARY COMMENTS 119
Boyer's UCSF Laboratory 119
Key Technologies for Biotechnology 121
Safety Measures 122
Boyer's Approach to Science 123
Defining Good Science 126
Writing and Publishing Papers 127
Self-Assessment 128

TAPE GUIDE 130

APPENDIX

A Biographical Information and Bibliography, Herbert W. Boyer 131
B Cartoon from a Slide Courtesy of Stanley N. Cohen 145
C Cloning Diagram from a Slide Courtesy of Stanley N. Cohen 146
D Documents Concerning Potential Biohazards
Singer-Soll Letter, *Science* Magazine, Sept. 21, 1973 147
Berg Letter, *Science* Magazine, July 26, 1974 148
"'Fail-Safe' Plan on Gene Research," *San Francisco Chronicle*, February 28, 1975 149
"Genetic Manipulation: Guidelines Issued," *Nature* Magazine, July 1, 1976 151
E UCSF Biosafety Committee
UCSF News Release on Creation of a Campus Biosafety Committee, October 5, 1976 154
Chancellor's Letter on Events in "Modern Biology," March 16, 1977 156
F Sculptures Depicting the Initial Meeting of Swanson and Boyer in Late 1975, with the Living Originals 159
G UCSF News Release on the pBR322 Incident, September 26, 1977 160
H UCSF News Release on Somatostatin, December 2, 1977 162
I Genentech News Release on Human Insulin, September 6, 1978 166
J UCSF/Industry Relations, Circa 1980 172
K Genentech, Inc.
*Time* Magazine Article, October 20, 1980, on Genentech's Initial Public Offering, 1980 177
"Genentech's Herbert Boyer," *Time* Magazine Cover, March 9, 1981 178
Excerpt from 1981 Genentech Annual Report 179
L Selected Honors
National Medal of Technology, 1989 181
National Medal of Science, 1990 183

INDEX 185

BIOTECHNOLOGY SERIES HISTORY--Sally Smith Hughes, Ph.D.

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

In 1996, a long-held dream of The Bancroft Library came true with the launching of its Program in the History of the Biological Sciences and Biotechnology. For years, Bancroft had wished to document the history of the biological sciences on the Berkeley campus, particularly its contributions to the development of molecular biology. 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. These materials support Berkeley's History of Science faculty, as well as scholars from across the country and around the world.

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 nor its origins in academic biology. For a decade, the staff of the Regional Oral History Office had sought without success to raise funds for an oral history program to record the development of the industry in the San Francisco Bay Area. When Charles Faulhaber arrived in 1995 as Bancroft's new director, he agreed to 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. He too saw the importance of documenting 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. Preservation of this history was obviously vital for a proper understanding of science and business in the late twentieth century.

Bancroft was the ideal location to launch such an historical endeavor. It offered the combination of experienced oral history and archival personnel, and technical resources to execute a coordinated oral history and archival program. It had 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 had longstanding cooperative arrangements with UC San Francisco and Stanford University, the other research universities in the San Francisco Bay Area. The history of biotech project was to provide a basis for continuing collaboration among the three institutions in the documentation of recent science and technology through oral history and archival collection. The only ingredient missing was funding.

In April 1996, the dream became reality. Daniel E. Koshland, Jr. provided seed money for a center at The Bancroft Library for historical research on the biological sciences and biotechnology. Thanks to this generous gift, Bancroft has begun to build 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. One of the first steps was to create a board composed of distinguished figures in academia and industry who 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.

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. In February 1998, Robin Chandler, head of UCSF Archives and Special Collections, completed a survey of corporate archives at local biotechnology companies and document collections of Berkeley and UCSF faculty in the biomolecular sciences. The ultimate aim is to ensure that personal papers and business archives are collected, cataloged, and made available for scholarly research.

## Project Structure

With the board's advice, Sally Hughes, a science historian at the Regional Oral History Office, began lengthy interviews with Robert Swanson, a co-founder and former CEO of Genentech in South San Francisco; Arthur Kornberg, a Nobel laureate at Stanford; and Paul Berg, also a Stanford Nobel laureate. A short interview was conducted with Niels Reimers of the Stanford and UCSF technology licensing offices. These oral histories build upon ones conducted in the early 1990s, under UCSF or Stanford auspices, with scientists at these two universities.[1] The oral histories offer a factual, contextual, and vivid personal history that enriches the archival collection, adding information that is not usually present in written documents. In turn, the archival collections support and provide depth to the oral history narrations.

---

[1]Hughes conducted oral histories with Herbert Boyer, William Rutter, and Keith Yamamoto of UCSF, and with Stanley Cohen of Stanford. To date, the first volume of the oral history with Dr. Rutter is available at the Bancroft and UCSF libraries; transcripts of the other interviews are currently under review by the interviewees.

## Primary and Secondary Sources

This oral history program both supports and is supported by the written documentary record. Primary and secondary source materials provide necessary information for conducting the interviews and also serve as essential resources for researchers using the oral histories. The oral histories also orient scholars unfamiliar with the field or the scientist to key issues and participants. Such orientation is particularly useful to a researcher faced with voluminous, scattered, and unorganized primary sources. This two-way "dialogue" between the documents and the oral histories is essential for valid historical interpretation.

Beginning with the first interviews in 1992, the interviewer has conducted extensive documentary research in both primary and secondary materials. She gratefully acknowledges the generosity of the scientists who have made their personal records available to her: Paul Berg, Stanley Cohen, Arthur Kornberg, William Rutter, and Keith Yamamoto. She also thanks the archivists at Bancroft, UCSF, and Stanford libraries, and personnel at Chiron, Genentech, and Stanford's Office of Technology Licensing, for assistance in using archival collections.

## 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.[1] Yet these acknowledged weaknesses of oral history, particularly its subjectivity, are also its strength. Often individual perspectives provide information unobtainable through more traditional sources. Oral history in skillful hands provides the context in which events occur--the social, political, economic, and

---

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

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.

## Update, September 2001

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. At an initial meeting of Genentech and Library personnel in November 2000, it was agreed that the initial phase of the Genentech-supported project in the company's twenty-fifth anniversary year should focus on oral histories

with current and former Genentech employees. Archival collection, on the other hand, was designated as a long-term process because of the greater necessity to gather oral documentation while minds are clear and because of Genentech's present need to retain many corporate documents for legal and other reasons.

On October 15, 2001, The Bancroft Library will celebrate Genentech's twenty-fifth anniversary and acknowledge its generosity to the Program by formally presenting the oral histories of Herbert W. Boyer and Robert A. Swanson, the company's founders. Oral histories are currently in progress with the following individuals presently or formerly at Genentech: David Goeddel, Arthur Levinson, Fred Middleton, Richard Scheller, and Daniel Yansura. Oral histories are also completed or in progress with individuals at Chiron Corporation and Tularik, Inc. The next phase will expand documentation to other biotechnology companies.

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://www.lib.berkeley.edu/BANC/Biotech/.

Sally Smith Hughes, Ph.D.
Historian of Science

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
October 2001

October 2001

## 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

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

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

"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
David Goeddel
Daniel Koshland
Marian E. Koshland retrospective
Arthur Levinson
Fred Middleton
Richard Scheller
Keith R. Yamamoto.

INTRODUCTION by J. Michael Bishop

It was Herb Boyer's bad luck that Arnold Palmer was born in Latrobe, Pennsylvania. Otherwise, Herb would be the most famous person to hail from that remote part of the universe. No matter: there is glory enough to go around. Arnie may have swung a golf club well and led a small army around when he was in his prime. But he never invented a revolutionary technology nor founded an entire new industry, and he will never see his accomplishments produce immeasurable advances in human health and welfare. All those credits go to Herb Boyer. Granted, Herb had a little help from others, as he tells in the pages that follow. But he was the constant in the story.

I first met Herb when I arrived at the University of California, San Francisco (UCSF) in 1968 as a newly minted assistant professor. He had preceded me by little more than a year, so we were immediate brethren in the joys and deprivations of being junior faculty. My starting salary was 14,000 dollars, Herb's may have been even worse--he was not then much of a bargainer. In the years to come, however, he would do vastly better than I in compensating for our impecunious start. (It may be fantasy, but I recall that Herb did offer me one main chance--the opportunity to be an early investor in Genentech; I declined--it seemed a dubious scheme to me.)

Herb was (and remains) twice my size, he was enormously friendly, and he knew ever so much more about how to do research than I did. I would have been a fool not to have liked him and not to have listened to him. I did both and profited immensely. How could I return the favor? Herb says here that I "provided some scientific stimulation" and "was just good company." No one could ask for better praise (although the qualifiers "some" and "just" give me pause for thought).

I was chagrined to read in these interviews that certain unnamed denizens of the floor on which I worked at UCSF banished Herb because of fear that the bacteria required for his experiments would contaminate the premises, damaging academic careers. Herb was consigned, instead, to inferior quarters, bereft of virtually all professional amenities. Could I have been among the baleful lot that issued the edict? Certainly not! Herb was well ensconced in his decrepit exile by the time that I arrived in San Francisco. Herb took at least modest revenge for his ostracism, destroying several pieces of the expensive equipment that he regularly borrowed from his oppressors. And since like attracts like in science, one of his early graduate students managed to earn the sobriquet "auto-destruct."

However poor his quarters, Herb did wondrous things, and for a while, no one knew. In fact, for much of his career, he remained "something of an outsider," as he describes himself. I certainly did not appreciate the astonishing potential of what Herb was doing in those early years. Nor did he, by his own admission. He was simply following a trace of curiosity that originated in his fascination with genetics as a high school student; that first materialized in his graduate thesis (a bold but doomed effort to ascertain the nature of the genetic code by mutagenesis alone, anticipating by several years the more successful experiments of Sydney Brenner and Francis Crick); that evolved into an interest in how chemical modifications of DNA can change the behavior of genes; and that culminated in path breaking studies of restriction endonucleases, the development of recombinant DNA, and the launching of the biotechnology industry.

Is there anyone in modern biology who does not know about that fateful evening in a Honolulu delicatessen, when Herb Boyer and Stanley Cohen sealed the deal that led to the cloning of DNA? Why is it that no one ever names the place? I searched in vain for it even in these interviews. Wherever it occurred, the moment was so portentous that it is now enshrined in sculpture on the Genentech campus. And how easy it is to forget the daring of what came next: move genetic material from one species to another, across billions of years of evolution, and have it propagate. It proved to be ridiculously easy, once a few technical problems were solved. The first sign of success overwhelmed Herb: "I can remember tears coming into my eyes, it was so nice." I was just down the hall when this happened, I am certain, but I missed the moment.

It was nice, it was powerful, and for some, it was worrisome. Alarms sounded. What mischief might ensue such meddling with the natural order? Before long, the research community had implemented a voluntary moratorium on research with recombinant DNA until the issue of safety could be resolved. In December of 1974, concerned parties met at the Asilomar Conference Center in Pacific Grove, California, and drafted the first of several sets of guidelines by which recombinant DNA could be pursued. The matter was soon in the hands of the federal government, and molecular biologists knew for the first time the full force of bureaucracy.

For Herb Boyer, the Asilomar conference was a "nightmare," an "absolutely disgusting week," and the biohazard committees that the conference sired, "an incredible waste of time and money." Harsh words, but I too was at Asilomar, and I can vouch for the distemper of the event. Unlike Herb, however, I saw value in the caution with which the research community proceeded, even though I too was never convinced that we faced any substantive hazard from recombinant DNA. Cynics now say that much of

the fuss disappeared once molecular biologists belatedly came to understand the fundamentals of bacterial ecology, as authentic microbiologists had long understood them. Twenty years downstream, I do not believe that the delay cost humanity very much by way of progress, and it helped preserve some of the prerogatives of the scientific community. Herb Boyer puts it more bluntly: "In five years, it probably didn't make a hell of a big difference."

Having disturbed the precepts of the natural order, Herb proceeded to rattle the precincts of the academic fraternity. According to his account, it all began because he was second on Bob Swanson's alphabetical list of individuals who might have intellectual property that would be useful in the commercialization of recombinant DNA. (The first person on the list apparently said no. Herb suspects that the naysayer was Paul Berg, but I have it on good authority that this is not correct.) Swanson got no farther down the list. Genentech was born.

Those who believe that Herb Boyer played only a casual role in the creation of Genentech should read these interviews, because they provide clear evidence of the thoughtful attention that Herb gave to the science, the personnel, and the ethos of the infant company. His imprint persists to this day, making Genentech one of the premier employers-of-choice among scientists seeking a career in biotechnology, and one of the crown jewels of an industry that seeks to advance human health and welfare.

Commercialization of biological discoveries was far from novel at the birth of Genentech: Big Pharma had been doing it for a long time. But for a member of the academic community to be so intimately involved, that was a sea change. No one had thought much about the rules for how this might be done. So there were repercussions, particularly among the faculty of UCSF --a hue and cry over potential conflicts of interest. It was a harrowing time for Herb Boyer, best grasped through his own words in these interviews.

Times have changed, as Boyer ruefully notes. Most of his former critics now traffic with industry as if it had always been so. But make no mistake, the issues of professional conduct that arose during the infancy of biotechnology persist today. We have still to perfect the rules of play, even as the demand mounts to accelerate the transformation of biomedical discoveries into practical applications, and even as the academy grows ever more eager and needful for the revenues that commercialization can bring.

Herb Boyer emerged from Latrobe as a naif. That was to become a precious legacy. He consistently tried big things without knowing whether they could or should work. His graduate thesis was an impossible undertaking with a germ of genius. His decision to purify and characterize restriction enzymes brought him into competition with some of the most formidable scientists on the face of the globe. His partnership with Bob Swanson was driven mainly by a desire to acquire more funding for his laboratory and junior colleagues--the personal financial gains that lay in the offing were beyond his "wildest dreams". His desire to use recombinant DNA for the production of human proteins was fueled in part by the possibility that his older son might require an extremely scarce medication, growth hormone. His expectation that such production could be scaled up to industrial levels had no basis in fact. Herb's explanation: "I think we were so naive, we never thought it couldn't be done."

In due course, Boyer lost his naiveté and gained celebrity. He was awarded the National Medal of Technology and the National Medal of Science, in successive years. He has been honored as an inventor and as a scientist in many other ways. He has been featured in *People* magazine. Through it all, Herb has remained bemused and unpretentious. This is not to say that he is oblivious to his opportunities. I once asked Herb to identify his favorite site for fly fishing. I expected a recognizable name from somewhere in North America, but Herb named a river in Patagonia. So far as I knew at the time, the last scientist to visit Patagonia had been Charles Darwin.

As a scientist, Herb was generous with precious reagents: some say that he shipped off the makings of a Nobel Prize in mailing tubes. As a person of wealth, he has been generous with his philanthropy. But he has become more discriminating with his philanthropy than he was with his reagents, and his discrimination reflects his loyalties. Seeking postdoctoral training many years ago, Herb was rebuffed at Stanford but accepted at Yale. It is Yale that now boasts a Boyer Hall, not Stanford. Perhaps his most renowned act of generosity was to direct all his personal income from the patents on recombinant DNA to his department at UCSF. (I hear tell that Stanford again did not fare as well, but that would not have been Herb's doing.) The eventual yield was 52 million dollars, to be used for graduate education and other good purposes at UCSF--all this above and beyond the university's direct share of the patent income. A portion of the UCSF Medical Center also bears the Boyer name in recognition of an additional gift.

Herb Boyer made another, more recent discovery: "There is a life after science." He retired from the UCSF faculty in 1991. Pursuing his

personal mantra to "lighten up," he has been patron to both a repertory theatre and a formula-one racing team (the latter in support of that older son, who never did require growth hormone); he learned to fly and pursued his romance with classic cars; he has attempted to emulate Arnold Palmer on the golf links; and he has fished in every hemisphere. His story is archetypically American--a testimony to the power of egalitarian opportunity, individual freedom, and noble ambition. And as the story is told here, it ends in a quintessential Boyerism: "So that's about all I have to say." It is said well and it should be read.

J. Michael Bishop
Chancellor
University of California, San Francisco

San Francisco, CA
September 26, 2001

INTERVIEW HISTORY--Herbert W. Boyer

Most people are lucky to make their mark in one area of professional life. Herbert W. Boyer has made his in three: science, business, and the law. In science, he and Stanley N. Cohen of Stanford University are celebrated for their development of recombinant DNA in 1973-1974. In the business world, Dr. Boyer is remembered as co-founder, with Robert Swanson, of Genentech, the first company founded on recombinant DNA technology and the harbinger of a new industry. And in the legal field he is associated with the Boyer-Cohen cloning patents which set precedents for intellectual property law in biotechnology. Although Boyer mentions the patents in this oral history, his interest lies in the basic science of recombinant DNA and the formation of Genentech.[1]

A highlight of this oral history is Boyer's detailed narration of the research up to and including the critical experiments with Stanley Cohen, culminating in the technology subsequently named recombinant DNA. (The term does not appear in the three papers published in 1973-1974 by the Boyer and Cohen laboratories.) In addition to details of the science, Boyer addresses the biohazards controversy and the now-famous Asilomar Conference on Recombinant DNA Molecules of 1975 and the safety precautions for recombinant research which UCSF and other research universities adopted in Asilomar's wake.

Another high point is Boyer's discussion of events leading to the formation of Genentech in 1976. He prefaces the oft-told tale of his first meeting with Robert Swanson with the less-known fact that he had already envisioned commercial applications of recombinant DNA before ever meeting the young entrepreneur. He goes on to describe why somatostatin, rather than insulin, became Genentech's first project. There were some tense moments, as Robert Swanson's oral history also describes, in which it was not clear that recombinant DNA would prove to be useful in pharmaceutical production[2]. The successful cloning and expression of the human gene for somatostatin had heartening repercussions for the future of an industry based on the new genetic technologies and for the struggling young company which Boyer and Swanson had just founded.

---

[1]The Cohen-Boyer patent is discussed at length in the oral histories in process with Stanley N. Cohen and Thomas D. Kiley, first general counsel at Genentech. (At Stanford it is the "Cohen-Boyer" patent; at UC the "Boyer-Cohen" patent.)

[2]Robert A. Swanson, "Co-founder, CEO, and Chairman of Genentech, Inc.," an oral history conducted in 1996-1997 by Sally Smith Hughes, Ph.D., Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2001.

The Oral History Process

I conducted five interviews with Dr. Boyer in 1994. It was almost a year after our first meeting before Dr. Boyer was ready to schedule the initial interview. Although he had retired from UCSF in 1991, he was busily engaged in activities ranging from board memberships to fishing trips to attending a son's car races around the country. Once Dr. Boyer had agreed to the first interview, scheduling subsequent sessions fell easily into place. Despite aversion to self-aggrandizement, he gave every appearance of being fully engaged in and enjoying the interview process.

The interviews were conducted in the Boyer home in Mill Valley with its spectacular outlook from the slopes of Mt. Tamalpais. (In recent years, Dr. Boyer and his wife Grace have moved to Rancho Santa Fe in southern California to be close to one son and a new grandchild.) The walls of the living room where we sat were hung with modern art and embellished with sculpture, guarded, using the term loosely, by Ralph the remarkable cat. Although Dr. Boyer projected a "laid-back" California manner, underlined by his glowing tan and attire of slacks and short-sleeved shirt, his answers were thoughtful, direct, and at times technical. For reasons explained in the oral history, he has always kept his involvement at Genentech at arm's length, although he continues to be a member of its board of directors.

I did the initial editing of the interview transcripts and sent them to Dr. Boyer in 1994. Because of other obligations, he did not review the transcripts for some years. In 1996, I returned to my permanent position at UC Berkeley and began work on the Bancroft Library's Program in the History of the Biological Sciences and Biotechnology. Nancy Rockafellar at UC San Francisco and I at UC Berkeley revived the Boyer project in 1998-99, with Dr. Boyer's subsequent agreement that the interviews would be produced in both the UCSF oral history series and in the Bancroft Library's Program in the History of Bioscience and Biotechnology at UCB. Willa Baum, former director of Berkeley's Regional Oral History Office and Kathy Zvanovec-Higbee, also of ROHO, adeptly coordinated work on the two campuses. The resulting oral history volumes have identical pagination but different accompanying pages, consistent with the standards of each institution. I am grateful to Dr. Boyer for the time and energy expended on this project and to Cookie Lupacchini for graciously smoothing the way. We particularly thank Chancellor Bishop for writing an informative and graceful introduction to an oral history of a friend and former colleague. Shannon Page served as expert transcriptionist. I also thank the Genentech Foundation for Biomedical Science which underwrote the interviews and Genentech, Inc. for its support of final production of the UCSF and UCB volumes.

Dr. Boyer's modest and revealing account, when used with the oral history in process with Dr. Cohen, provides the most complete description in existence of the origin of recombinant DNA technology and the nature of the

collaboration of the Boyer and Cohen laboratories. In addition, with the availability of the Boyer and Swanson oral histories, we have the first comprehensive history in the words of the founders of the genesis and early years of Genentech.

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

Sally Smith Hughes, Ph.D.
Historian of Science

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
October 2001

# Curriculum Vitae

Herbert W. Boyer

Birthdate: July 10, 1936
Birthplace: Derry, Pennsylvania

## Education

| | | |
|---|---|---|
| St. Vincent College, Latrobe, PA | B.A. | 1958 |
| University of Pittsburgh, Pittsburgh, PA | M.S. | 1960 |
| University of Pittsburgh, Pittsburgh, PA | Ph.D. | 1963 |
| Yale University, New Haven, CT | Postdoctoral | 1963-66 |

## Honors and Societies

| | |
|---|---|
| V.D. Mattia Award, Roche Institute of Molecular Biology | 1977 |
| Doisy Lecturer, University of Illinois | 1979 |
| Fellow, American Academy of Arts and Sciences | 1979 |
| Albert Lasker Basic Medical Research Award | 1980 |
| Honorary Doctor of Science Degree, St. Vincent College | 1981 |
| American Academy of Achievement, Golden Plate Award | 1981 |
| California Inventors Hall of Fame | 1982 |
| Industrial Research Institute Achievement Award | 1982 |
| National Academy of Sciences | 1985 |
| Distinguished Alumni Award, University of Pittsburgh | 1987 |
| Fellow, American Association for the Advancement of Science | 1988 |
| Cetus Corporation Award for Research in Biotechnology | 1988 |
| Moet Hennessy-Louis Vuitton Prize, Biotechnology Prize | 1988 |
| City of Medicine Award, Durham, NC and Duke University | 1988 |
| First National Biotechnology Award | 1989 |
| National Medal of Technology | 1989 |
| National Medal of Science | 1990 |
| Helmut Horten Research Award | 1993 |

| | |
|---|---|
| Lemelson-MIT Prize | 1996 |
| Biotechnology Heritage Award | 2000 |

**Professional Positions Held at the University of California, San Francisco**

| | |
|---|---|
| Professor Emeritus | 1991-present |
| Professor, Department of Biochemistry and Biophysics | 1976-1991 |
| Investigator, Howard Hughes Medical Institute | 7/76-6/83 |
| Director, Graduate Program in Genetics | 7/76-9/81 |
| Associate Professor of Biochemistry, Dept. Of Biochemistry & Biophys. | 12/75-6/76 |
| Associate Professor of Microbiology, Dept. Of Microbiology | 1971-1975 |
| Assistant Professor, Department of Microbiology | 1966-1971 |

**Academic Committees and Extramural Activities**

| | |
|---|---|
| Medical Student Research Committee, UCSF | 1973-1976 |
| Faculty Council, School of Medicine, UCSF | 1975-1976 |
| Co-Founder and Board of Directors, Genentech, Inc. | 1977-present |
| Consultant to UNIDO | 1980-1982 |
| American Academy of Achievement, Executive Board | 1982-1986 |
| Board Member, Radiology Research and Education Foundation | 1985-1995 |
| Board, Marin Theatre Company | 1986-1995 |
| Board Member, St. Vincent College | 1986-1995 |
| Dean's Council, Yale University School of Medicine | 1989-1997 |
| President's Circle, National Academy of Sciences | 1989-present |
| Director, UCSF Foundation | 1992-1995 |
| Member, UCSF Capital Campaign Committee | 1992-1995 |
| Board Member, Allergan Corporation | 1994-present |
| Chairman of the Board, Allergan Corporation | 1998-present |
| Member of the Board of Trustees, Keck Graduate Institute | 1999-present |
| Member of the Board of Trustees, Scripps Research Institute | 1999-present |

INTERVIEW WITH HERBERT W. BOYER

## I EDUCATION

[Interview 1: March 18, 1994]##[1]

### St. Vincent's College, Latrobe, Pennsylvania

Hughes: I know where you were born and raised, but for the sake of the recording, please tell me.

Boyer: I was born in western Pennsylvania in 1936, grew up in a small town there, Derry, Pennsylvania. Went to public schools, and attended a liberal arts college nearby in Latrobe. We were known as day hops if we commuted from our homes to the school, St. Vincent's College. I graduated from St. Vincent's in 1958, and went on to the University of Pittsburgh for a graduate degree in microbiology.[2]

### Graduate Student, University of Pittsburgh, 1958-1963

#### Interest in Microbial Genetics

Hughes: Explain how you became interested in microbiology.

Boyer: Well, I had more of an interest in genetics as an undergraduate, and even in high school I had an interest in genetics from the biology course we had. When I applied to the University of Pittsburgh for graduate school, I expressed an interest in genetics and was told that there was a new faculty member there, Ellis Englesberg, who was interested in microbial genetics. It was a new, hot field at that time, and I found it to be interesting. I went to talk to him, and became very much interested in what he was doing. So that's how I got into microbiology.

Ellis Englesberg was at the University of Pittsburgh for a number of years after I left, and then he went to UC Santa Barbara. I think he

---

[1]## This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

[2]For more on Herbert Boyer's early life see his oral history, recorded May 29, 1975, in the Recombinant DNA Controversy Oral History Collection, Institute Archives and Special Collections, MIT.

must be retired by now, but I couldn't say for sure. So actually, the University of Pittsburgh had a department of biological sciences, and then they had divisions within that, including a microbiology division. So I couldn't tell you exactly whether the degree was in microbiology or biological sciences with a specialty in microbiology, but essentially the training was in microbiology.

Hughes: What was happening in microbiological genetics at that time? It was a pretty hot period, wasn't it?

Boyer: Well, it was. It was the post-Watson-Crick discovery era.[1]

Hughes: You were too young to have their discovery make an impression?

Boyer: No, it did make an impact on me. When I was in undergraduate school, I was taking a physiology course, and there was a new textbook which seemed very interesting. Maybe it was just the shiny new pages more than anything else. But the textbook was Geise's new *Cell Physiology*. During the semester, the physiology course curriculum required that each student, and there were maybe fourteen or fifteen students in the class as best as I can remember, give a half-hour lecture or so on one of the chapters. So we were to read and prepare ourselves.

I can't remember whether I was assigned or whether I chose the chapter which dealt with DNA as a genetic material, which sort of summarized the Watson-Crick discoveries and some of the other pertinent findings of the time. I thought it was great. I was so enthusiastic about it, I got a pretty good grade on the lecture. But that was my first introduction to DNA and the Watson-Crick era.

Hughes: Did you follow it from then on?

Boyer: Well, I had a strong interest. We had a great old professor who was a Benedictine--St. Vincent's was a Benedictine liberal arts school--and this guy was just so great, very kind and thoughtful and a dedicated man. I remember we talked about the genetic material. One time, in a laboratory setting, he was discussing the nature of the genetic material, and he expressed his belief that it had to be protein. I can

---

[1]James Dewey Watson and Francis Harry Compton Crick proposed a "double helix" structure for the DNA molecule in 1953. In 1962 they were awarded the Nobel Prize in Physiology or Medicine.

remember him talking about how proteins had to be the genetic material, and he talked about viruses replicating and so on and so forth. This was probably in 1956. So the Watson-Crick discovery hadn't made the impact into the small liberal arts schools and other schools which didn't have sophisticated faculty doing research.

Hughes: Of course, the hypothesis that the genetic material was protein wasn't a crazy idea.

Boyer: No, no, it had been proposed. But then when I read this chapter, it all made sense that DNA was the genetic substance. These were the questions that were floating around at the time.

### The Genetic Code

Hughes: What year did you give the chapter presentation?

Boyer: That would have been 1957, I believe.

Hughes: So the code had not been broken.

Boyer: No. When I went to graduate school, the genetic code was a focus of investigative activity and something in which I was interested. My Ph.D. dissertation research was directed toward that end.[1] It was an ambitious project, and a lot of people were attempting to get at the nature of the code at that time by doing what we called fine structure genetic analysis. Essentially we just tried to saturate a gene with mutations and determine the linear arrangement of mutational sites and characterize them as best as possible--the size of the gene compared to the protein, et cetera, et cetera. It was a laborious and extremely difficult task.

Hughes: Which you didn't realize when you chose the topic?

Boyer: Well, of course not. [laughs] You don't want to take on easy projects. But it was very exciting.

Hughes: Did it work?

---

[1]Herbert W. Boyer, "Studies of Base-Analogue Induced Mutations in a Small Region of the L-Ribulokinase Structural Gene of *Escherichia coli*" (Ph.D. diss., University of Pittsburgh, 1963).

Boyer: Eventually work? It would have taken many, many years from that approach. From what we know today, it might, but much of what we know today is based on knowing the genetic code from other means, so it's hard to say we would have ever come to the same conclusions that we have at this particular time.

The approach involved using what were described as specific mutagens, mutagens which one thought caused certain changes in the genetic material. You would study the mutation rates, you would isolate mutations, determine their linear arrangements, and then you would try to analyze revertants to further analyze what the initial mutational change might have been. So if you could mutate it with one mutagen, and then reverse it with another, that might be some confirmation of the type of change. If you converted it with the mutagen that was thought to just cause AT [adenine-thymine] to GC [guanine-cytosine] changes, then you should be able to revert it with one that was supposed to just cause GC to AT changes. So it was that type of approach, and it involved a lot of work, long hours, isolating mutants and characterizing them.

Hughes: Was this in the division of microbiology?

Boyer: Yes.

Hughes: You could have been in a lot of places, couldn't you?

Boyer: There were a number of laboratories interested in this. I couldn't tell you how many, but the individual who sort of spearheaded this particular approach was a phage geneticist by the name of Seymour Benzer, one of the original members of the molecular biology school.

## Mentors and Colleagues

Hughes: Is that where you had gotten the idea?

Boyer: I think I got the idea because I was told about it by my advisors and my mentors.

Hughes: They were doing this sort of research?

Boyer: Yes. Well, Ellis Englesberg was interested in control mechanisms, and he was using a microbial system which had multiple steps in the pathway. One could control by the substrate the amount of these

enzymes being present. They were inducible enzymes. So he was working on this system and mapping mutational sites, doing the enzymology and so on and so forth.

Then there was another young assistant professor who came into the department whose name was Roger Weinberg, and he wanted to use this particular system to try to get at the genetic code, as I just described in brief outline. So the two of them worked together, and I primarily worked with Roger Weinberg on the mutational side of things. But we did a lot of collaborative work with Ellis, and he was part of the immediate mentorship that I had.

He's a very forceful man, very critical. He could put the whip to you pretty good. He used to be very critical of people who lived in the suburbs of Pittsburgh and commuted back and forth to the university, rather than living in the tenements nearby and spending all their time working. But most of us worked pretty long hours.

Hughes: You were not commuting at that stage?

Boyer: No, we lived in Pittsburgh. Within I think the last year I was in graduate school, we moved out from Pittsburgh, because my wife Marigrace was working at Mellon Institute near Monroeville.

Hughes: When did you get married?

Boyer: I got married after my first year of graduate school [1959].[1]

## The Department of Microbiology at Pittsburgh

Hughes: By then, did most departments of microbiology have a genetic, phage approach? They weren't just doing classical microbiology?

Boyer: I don't know. This department had a large contingent of more traditional microbiologists. They weren't of significant reputation. But I remember one individual who was interested in crown gall. You can cause tumors in plants with bacteria. I remember going to seminars by this guy. Years later, it became one of the crucial things, with identification of the causal agent as actually a plasmid within a

---

[1]Herbert W. Boyer and Marigrace Hensler were married in 1959.

bacterium which causes the tumor, and it's a pathogenic effect. That particular plasmid has served as the basis for a lot of the plant genetic engineering that is taking place today.

Hughes: Little did he know.

Boyer: Well, he didn't have the tools or the background. It took years to find out what was going on there. The fellows that I worked with were just continually trying to get at this guy. They couldn't believe that it was a bacterium and were always trying to shoot down his research. But it never went anywhere because he just didn't have the tools or the resources. It wasn't a subject of interest at the time to funding agencies. Plant biology didn't attract a lot of research unless you were doing plant tissue culture. All he did was rub dirt on the plants, and they would get tumors.

Hughes: It wasn't cutting edge.

Boyer: That's right.

Hughes: Well, what about funding for your field, for genetics?

Boyer: Well, this was an era when the funding was just starting to take off. I can remember, Englesberg had some funding from the Naval Research Laboratories to do a study with *Salmonella typhimurium*, and he was doing the same type of genetic analysis on it as he was with the *E. coli* system that I alluded to before. He wanted to get out of the *Salmonella* system. First of all, you could get sick working with it. I remember one guy who did come down with some typhoid symptoms and had to be treated, and he worked in this lab.

So Ellis eventually phased that out. But he had funding from NIH and the Naval Research Labs, and I got a research fellowship. I was paid $2,500 a year to work in the lab.

Hughes: And you could really make it on that amount?

Boyer: Just about. With a little bit of help from my wife, we could do it.

Hughes: She's a scientist?

Boyer: She was a scientist, yes. She had an undergraduate degree in science, and she worked in the Mellon Research Laboratories. They primarily

did contract work with companies to test various chemicals for their safety, things like that.

Hughes: So she was a chemist?

Boyer: No, she was a biologist.

Hughes: Do you want to say something about politics?

Boyer: I was apolitical at that time. Really had no interest in politics. My dad was a Democrat, and in the high school mock elections, I always voted Democratic. But other than that, I really couldn't have cared less.

## Postdoctoral Fellow at Yale University, 1963-1966

### Interest in Bacterial Plasmids

Hughes: Is the next step then Yale?

Boyer: After University of Pittsburgh, yes. I did a postdoctoral fellowship at Yale.

Hughes: How did that come about?

Boyer: When I was finishing my graduate degree [1963], there were a lot of people doing interesting things. So I started to try and identify people in places where I'd like to go do a postdoctoral fellowship. I had developed an interest in bacterial plasmids.

Hughes: How had you developed that interest?

Boyer: Largely through reading scientific papers, attending seminars by visiting scientists. There was a scientist, Dr. Charles Brinton, at Pittsburgh who had a peripheral interest in plasmids.

Hughes: Why did they intrigue you?

Boyer: Well, they were small mini-molecules. They were like mini-chromosomes. They could be manipulated, they were fun, and they carried a number of genetic determinants that could easily be utilized. Plasmids were shown during this period of time to be the causative agent of sexual conjugation in bacteria. These elements were transferred from one cell to another, had similarities with viruses, and

things of that sort. So they were interesting from a phenomenological, biological point of view.

And I had an interest in recombination of DNA based on what I was doing with the mapping of these mutations. So I applied to Charlie Yanofsky's laboratory at Stanford, and he didn't have room for me. This was a polite way of saying no, I guess. I had an opportunity to go to the University of Pennsylvania with a scientist who was doing some very nice protein work, looking at mutations in a particular protein and the suppressor mutations affecting those.

But I decided to go to Yale because of the interest in plasmids. Yale's an interesting place, intellectually. And it was a lot different than it is today. The nature of New Haven, for example, was much different than it is now. But the scientist who offered me a place at the University of Pennsylvania, went to Yale the year after I went to Yale.

Hughes: Were you going to Yale to work specifically with one particular individual?

Boyer: Yes, I went to work with a wonderful man, Ed Adelberg, who had just come back to Yale. He had done an undergraduate degree at Yale, and he got his Ph.D. there too, if I remember correctly. He had been at the University of California at Berkeley in the microbiology department there, and then he went to chair the department at Yale. A lot of old Yalies end up their careers there or go back at some point. He was just a wonderful guy, was very supportive.

## Postdoctoral Work on Gene Mapping of *E. coli* Strains

Boyer: The work I did there I brought with me from my graduate school research. The whole basis for my interest in research in the restriction and modification of DNA came from work that I did as a graduate student. I didn't know what it was at the time, but it was intriguing. I had independently discovered the effect on the conjugal transfer of bacterial DNA, so I always had a very personal relationship with this phenomenology.

Hughes: You had discovered restriction and modification?

Boyer: I didn't discover it; I had discovered a phenomenology which had as its basis restriction and modification of DNA. I didn't know that

until after I got to Yale and continued to do some research, and to read the literature and talk to people and finally put two and two together.

Hughes: Tell me a little more, what was the phenomenon?

Boyer: I detailed it a little in the "Winding Your Way Through DNA Symposium." I may have skipped over it because the time was short, but anyway, I've written about it.[1] I was doing the genetic analysis of these mutations in *E. coli*. The particular model system that Englesberg was using involved the fermentation of L-arabinose. It's a pentose sugar. We were isolating mutations in this array of genes involved in the fermentation of arabinose.

We got to the point where we were stymied by the techniques we were using to carry out recombination. We were using a form of recombination methodology called P1 transduction, which was just absolutely murderous. You had to grow bacterial viruses on all the mutant strains you had, carry out crosses, and it was not very efficient. So we all knew about bacterial conjugation, but the strain of *E. coli* that we were using didn't have a sexual conjugation system. The basis of that involved plasmids, which was how I got interested in plasmids.

But there was a related strain of *E. coli*, a more conventional strain called *E. coli* K-12, which had a conjugational system, and you could get high numbers of recombinants, very high frequencies--a thousand times better than what you could get with some of the P1 transduction types of conjugation. So I decided that what I would do is get hold of some *E. coli* Hfr strains, and use them to convert the B strains we had into a sexual conjugation system. We had to convert them into Hfrs and F-minuses, to use the terminology of the time.

So I wrote to the fellow that I went to do the postdoctoral fellowship with, Ed Adelberg, and asked him for some strains, which he sent. We corresponded, and he told me about them and gave me some information on them. So I started to convert the *E. coli* B strains into a sexual mode.

---

[1]Later work along these lines was pursued at UCSF. Herbert Boyer and Daisy Roulland-Dussoix, "A Complementation Analysis of the Restriction and Modification of DNA in *E. coli*," *Journal of Molecular Biology* 41 (1969): 459-472.

Hughes: Now that was just a cookbook sort of procedure?

Boyer: Yes, it was pretty much a cookbook. The way to do it had been published. It had not been described for converting the B strains. This had all been done in *E. coli* K-12.

So when I started to do this, I noticed a particularly reproducible result when I crossed the *E. coli* K-12 strains with the B strains. When the K-12 DNA would be donated to the female B strains, the efficiency of conjugation was severely reduced. And when I looked at the linkage of markers in the recipients, that also was greatly reduced. Then when I started doing some back crosses from some of the recombinants I did get, I found that particular effect totally disappeared.

Eventually, I mapped a gene on *E. coli* K-12 and *E. coli* B chromosome, which was responsible for that, and as it turned out it was very close to this arabinose gene locus that we had been studying. So when I was selecting for that, I would also bring in this other allele, because it was very close. So I had mapped this gene near the arabinose locus and several genes for threonine biosynthesis. I thought, well, this was pretty exciting, but it didn't have much to do with my dissertation research.

##

Boyer: After I had made the appropriate strains, I did a lot of fine structure mapping of the arabinose gene loci, and so on and so forth. We never really got anywhere with our attempts to break the genetic code, because right in the middle of all this, it was broken [laughs] by the groups at NIH by other means. But we continued because there was still an interest in the structure of genes, and what you could determine by doing recombination.

Hughes: So your ultimate goal had been to break the genetic code?

Boyer: As a cog in a wheel of a laboratory, yes. As a graduate student, you sort of adopt what your advisors are doing. You definitely have to have an interest in it, but I don't think that you necessarily have to have an overriding interest in what you're doing. But I was very interested. It was exciting doing research, to someone like myself who had nothing but instructional laboratory exposure before that. It was great. It was just a lot of fun.

Hughes: You were in a department of microbiology, but you were essentially doing genetics. Were you thinking of yourself as a geneticist?

Boyer: Yes, I didn't really think of myself as a microbiologist, because I wasn't. I had to take courses in microbiology, but I wasn't particularly interested in microbiology. Now, there were interesting aspects to it, and microorganisms are a very bizarre collection of living things that do weird things, and most people don't realize they exist. But no, I thought of myself as a geneticist, or perhaps more as a molecular geneticist, which had a better ring to it.

As Erwin Chargaff once said, "Molecular biologists are nothing more than people practicing biochemistry without a license." [laughter]

Hughes: He had a pretty sharp tongue, didn't he?

Boyer: Yes, he did.

## Evidence of DNA Restriction and Modification

Hughes: Tell me what happened when you went to Yale.

Boyer: Well, when I was at Yale, I got involved with a project in Ed Adelberg's lab. It was really tough. I didn't get too interested in it, and we didn't have a good handle on it. We had some observations. Remembering back on the nature of it, I think that we were actually looking at transposons, which was years before they really became understood.

But I had this strong interest in the observations I had made at the University of Pittsburgh, and I described them to Ed Adelberg, who had an interest in bacterial conjugation, and in fact had written a very nice review with John Clark at Berkeley on sexual conjugation in bacteria involving plasmids, et cetera, et cetera. So he was very interested in the observations I had made, and encouraged me to go on with this. Then when I made the correlation between the research findings and the restriction and modification of DNA and demonstrated that was the case, I published a paper while I was

there.[1] This was the first determination of the location of the genes for research and modification of the *E. coli* B strains and *E. coli* K-12 strains. And on the basis of my observations, I was able to show that the DNA that's transferred by sexual conjugation was restricted and modified, and that these were the effects that it had on the recombination frequencies and gene linkages.

What was important to what I did there at the University of Pittsburgh came from a paper published in 1962, but which I didn't see until after I got to Yale. It was a seminal paper by Werner Arber and Daisy Roulland-Dussoix in Geneva in which they were able to show that the end result of the restriction of DNA in phage systems was that the DNA was degraded into small pieces.[2] So the hypothesis was that the enzyme involved in restriction of DNA was an endonuclease which had the ability to recognize a unique sequence of DNA.

Hughes: And that was a new idea?

Boyer: Yes, that was a new idea, enough for a Nobel Prize for Werner Arber. So I became intrigued with the idea of trying to identify restriction endonucleases and the modification methylases, which would be a methylase also capable of recognizing unique sequences of DNA.

Hughes: Was it a logical extension to assume that different bacteria would have different endonucleases?

Boyer: Well, there was developing at the time an identification of and knowledge about different types of nucleases in bacteria. But all the ones that had been described at that time were pretty much random in their cutting of DNA. They would just break down the DNA to small pieces, and it involved no specificity other than they recognized DNA per se. There was no recognition of unique sequences of DNA.

So this hypothesis about there being these enzymes was appealing to me, and I thought they would be wonderful things to purify and study

---

[1]Herbert W. Boyer, "Genetic Control of Restriction and Modification in *Escherichia coli*," *Journal of Bacteriology* 88 (1964): 1652-1660.

[2]Daisy Dussoix and Werner Arber, "Host Specificity over Acceptance of DNA from Infecting Phage 1," *Journal of Molecular Biology* 5 (1962): 37-49.

and characterize because they were somewhat unique. At that time, there were just a few laboratories in the world working on restriction and modification of DNA. I had very little background in purifying enzymes. I had worked with enzymes as a graduate student and done assays and things like that, but I had never purified an enzyme. So I spent some time at Yale trying to learn how to purify enzymes.

Hughes: Were there people in the department who could teach that?

Boyer: Actually, I went across town to do that. I continued to do research in my own laboratory, but I would spend the days working with a faculty member, Bruce Carlton, across town in the Klein Biology Tower. We in the department of microbiology were in the medical school. Bruce had actually come from Charlie Yanofsky's lab and had experience in purifying and characterizing enzymes. So I went and worked with him and learned how to purify the enzymes.

At the same time, I was trying to establish an assay for a restriction endonuclease. There was no assay for such an enzyme; one did not exist, and we had to try to develop our own. I used to spend the evenings trying to do that, back in the microbiology department at the medical school.

Hughes: So the other groups hadn't come up with an assay either?

Boyer: No.

## DNA Recombination Research at Yale

Hughes: Were you in pretty close communication with the other laboratories?

Boyer: Not real close. There wasn't the same type of communication you have today. We didn't have e-mail, and telephone calls were expensive, and letters took a long time. As a graduate student and postdoc--in those days, anyway--you didn't make a lot of overtures to people who were unknown to you, with whom you didn't work. At least I was somewhat reticent about approaching people for an idea.

But at Yale people were extremely kind, and I always appreciated the camaraderie and fellowship at Yale. People were very helpful, and they would help me with things I was interested in, try to help me with design. The people there had a strong interest in DNA

recombination at a molecular level, and I was exposed to all that thinking. I think it was very important; that was sort of the beginnings of my interest in in vitro recombination of DNA, being exposed to that, and thinking about recombination--or thinking about restriction endonucleases. I thought that there might be some utility in having those enzymes to dissect plasmids and viruses.

So while my mentor was on sabbatical in Paris, I was doing this dual thing, learning how to purify enzymes and trying to work with restriction and modification of DNA assays. But oh, it was so frustrating, looking for ways to do this. I had not, for example, made radioactive DNA, which we eventually ended up doing at UCSF. We used that as an assay.

Hughes: Why not at Yale?

Boyer: We weren't set up for it in that particular laboratory, and there weren't a lot of people really doing it as far as I can remember. There were laboratories around the country that were doing that. I did make some radioactively labeled DNA, but it wasn't a phage DNA, which was what we really needed to do. So it just took some time--trial and error approaches to things.

Hughes: Do you think your lack of progress with the radioactive tagging relates to what you were saying about communication?

Boyer: I think that looking back on it, the thing you do is you go to somebody's lab who has done it and say, "Can I come to your lab for a week and learn how to do it?" Later on, that's what we used to do all the time. People would come to my laboratory or we'd go to another lab, and somebody would show us how, or somebody would give us things, or we'd give things to people.

But being a very naive postdoc and coming from an atmosphere like the University of Pittsburgh where we almost were a self-contained group, we didn't have a lot of colleagues that we interacted with.

Hughes: But the technology was there? People elsewhere had it?

Boyer: I can't remember exactly, but I don't think it was routine.

See, in the assay, we needed to be able to detect an enzyme that would make just a few breaks in the DNA. So we had to be able to

detect the conversion of a molecule of a given size to a molecule of a slightly smaller size so we could look at solubility. I remember spending many hours trying to do viscosity assays. Viscosity assays were just-- I found them to be abominable, just horrible. And there we had these old viscometers around the laboratory left over from God knows, and I got those out and tried to use them and set up a model system. It was just very hard to do.

Then the other problem, which we eventually found out, which we would never have been able to predict, is that the organisms and the type of restriction enzymes we were going after in those days were just terribly complex, structurally and enzymatically.

Hughes: They cut in too many places?

Boyer: No. It turns out that the cofactors at that time were extremely bizarre. In addition to divalent cations, the enzymes that we were focusing on required ATP [adenosine triphosphate] and S-adenosyl-L-methionine to be active.

Hughes: And you didn't know that at the time?

Boyer: Oh, we didn't know that. We were trying different things. There was some suggestion that it might require ATP, but the first observation of that was made by a group at Harvard, Matt Meselson and Bob Yuan. Then once we had that, we were able to-- But this was all at UC San Francisco. It took a while. And again, there weren't too many people actually trying to purify these enzymes, because there was still not a lot of interest there.

The phenomenology itself goes back to the very early days of virology—Frederick W. Twort and Felix d'Hérelle, the original phageologists. I can't remember which one it was, or both of them, who had made the observation that the ability of viruses to grow on a particular host bacterial strain was adaptable. That is, you infected a bacterium with a virus from another source, and it wouldn't grow very well, but if you took the progeny, they would grow better, and so on and so forth. These observations were in 1918 or 1920, something like that.[1]

---

[1]During World War I, London investigator Frederick W. Twort noticed that vaccinia virus could cause "glassy transformation" in bacterial cultures,

Hughes: With no explanation.

Boyer: No, there wasn't. In those days, people were still using Lamarckian type of thinking: it was just an adaptation. The phage just became adapted. Well, in a sense, the restriction and modification of DNA is--I wouldn't call it Lamarckian--but a phenomenology which sort of demonstrates the idea of Lamarckianism, although it really isn't.

And then a lot of the early pathogenic microbiology work, the typing of microbial strains and the identification of microbial strains of one type or another as being pathogenic, was done by phage typing, which had its basis in restriction and modification of DNA. It was these observations which, to the molecular biologists of the fifties, molecular geneticists, sort of indicated that maybe this is some sort of primordial Lamarckian mechanism. That's what got the attention of the molecular biologists in the fifties. Salvador Luria or Max Delbruck, or maybe both of them, got a few people interested in doing some experiments along these lines.

## II UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, 1966-1991

### Faculty Member, Department of Microbiology, 1966-1975

#### Deciding to Come to San Francisco

Boyer: When I was finishing up my postdoctoral tenure at Yale, I went to talk to Ed Adelberg about looking for a job, and got his advice. So I went to look at a few positions and opportunities. He said, "You know, there's a position opening up at UC San Francisco. A friend of mine, chairman of the department of microbiology, Ernie Jawetz--" Jawetz was a friend of Ed's; they were colleagues, of course, when Ed was at Berkeley. Ed and Ernie Jawetz and another guy had written a

---

eventually killing them. In his only publication on the subject, Dr. Twort noted that one explanation for this phenomenon was that he had identified a lethal virus of bacteria. In August of 1915, Canadian bacteriologist Felix d'Hérelle noticed clear "plaques" in bacterial cultures and began to work on this group of viruses which he named bacteriophages. He published his work in 1917 and continued to work on phage replication cycles and promoted bacteriophage therapy for bacterial illness.

microbiology textbook for medical students--I can't remember the name of the series.[1]

But anyhow, Ed said that there was a position opening up in microbiology at UCSF, and that he knew that the university was committed to developing the basic sciences at UCSF, and that there wasn't much there at this time. But he said, "You should look at it, and it would be an interesting opportunity to go there. It should be developing as a very good center for the basic sciences."

I had always wanted to come to California. I had tried to come earlier and go to Charlie Yanofsky's lab. I had read about California, and of course, was a movie fan and watched all the movies about California. So I came out to San Francisco for the first time, I think it was probably late '64, early '65, something like that.

It was a much different place than it is today. It was pretty exciting. I thought it was great. San Francisco was so different from the East Coast. California is so different from the East Coast. This was great. So we decided to come here.

## Teaching Medical Students

Hughes: I looked at the records in the Department of Microbiology, and I know that one of the conditions was that you agree to come in the fall of 1965 as a visiting assistant professor to teach a series of ten classes in microbiology for medical students. Do you remember?

Boyer: Yes.

Hughes: The medical class that year had been expanded, so additional teachers were needed. And then you went back to Yale and didn't officially come to UCSF as assistant professor until July of 1966.[2]

---

[1]Ernest Jawetz, Joseph L. Melnick, and Edward A. Adelberg, *Review of Medical Microbiology* (Los Altos, CA: Lange Medical Publications, 1954). This textbook, first published in 1954, went through nineteen editions. In 1998 it was entitled *Jawetz, Melnick and Adelberg's Medical Microbiology*.

[2]Ernest Jawetz., M.D., Ph.D., Department of Microbiology: Annual Report on Academic Year 1964/65. Records of the Department of Microbiology, UCSF. See

Boyer: Yes.

Hughes: Had you done much teaching at that point?

Boyer: No.

Hughes: Was that your first experience?

Boyer: No, I had done a little, mostly in laboratories. Graduate students were never required to learn how to teach or know anything about teaching. I was a horrible teacher. I guess I'd never had a great deal of interest in presenting lectures. I had to correlate with textbooks. I enjoyed teaching science better, enjoyed working with graduate students and postdoctoral fellows at the laboratory, and talking about experiments, criticizing experiments, interpreting data, that sort of thing. But teaching, particularly teaching medical students--God, I dreaded that. It just put the fear of God into me tc face that group of iconoclastic individuals. And they had no interest in bacterial genetics, and I didn't know how to make it interesting, didn't spend the time to learn how to make it interesting. It was a chore. It was something I thought, "Let's get it over with so I can get on doing research."

Hughes: Did you have to write those ten lectures?

Boyer: Yes, I did. And I couldn't tell you what they were about. But it was a little traumatic, dealing with this group. Giving a seminar is about the only type of teaching experience graduate students get; we always had to give a couple of seminars a year. We had seminar courses in which you'd take a particular scientific topic and each member of the class would present a particular research paper and discuss the background and results and so on. But you had an audience which had an inherent interest in what you were talking about, so you had their attention, and there was a lot of give and take.

This doesn't happen when you go into a formal classroom. These people going into microbiology, unless they're learning about pathogens and what causes disease, and if they're not thumping, probing, and listening [laughter] it's just not relevant.

You have to remember, at this time, we were just in the throes of curriculum revolt and reform, so it was extremely difficult for me. As I said, I know I was never a good teacher. Ernie Jawetz would take

---

also "Interview with Ernest Jawetz" (San Francisco: UCSF Campus Oral History Program, UCSF Library and Center for Knowledge Management, Archives and Special Collections, forthcoming, hereafter cited as UCSF Library).

me in and try to critique my presentation, and I thought, Oh, my God, oh, no. Hard on the old ego to be told, "Well, you better get it together here." I never did manage to get a handle on giving lectures.

Hughes: Were you forced to give lectures all the way through?

Boyer: Well, it was part of your responsibilities, yes. We gave some graduate courses and conducted seminar classes. Those were a little bit better.

### First Impressions of UCSF

Hughes: What did you find when you arrived in the Department of Microbiology?

##

Boyer: What did I find? Well, thinking back on it, I think of all the negative impressions I had, but I'm sure I also felt the excitement of having my first job, being independent, going off to do my own research, moving to a new city, and so on and so forth. It was exciting.

But I do remember some of the problems I had. I had been promised laboratory space in the new Health Sciences East [HSE] Building, on the fourth floor. When I got there, I found out I had been reassigned to the Medical Sciences Building. The reason was that the people in Health Sciences East were doing tissue culture work, and they didn't want anybody growing bacteria over there. So I got reassigned to these laboratories which, when you compared them to what they had in HSE--how can I say it? The labs in Medical Sciences weren't very well designed for doing the research that I was involved with. Essentially, the laboratories had been designed to stain slides of bacterial specimens and other pathogenic organisms.

Well, fortunately, we did have an autoclave, and that was about it. I had no cold room, which I would have had in the other building. There was no ice machine. Outside of the autoclave, there was no core facility available in the immediate vicinity of my lab. So in order to do any biochemistry or enzyme purification, I had to walk over to HSW or HSE and establish all my purification. Then, of course, the people there weren't too thrilled about me being there anyway. So it was extremely difficult.

We had to go over to Health Sciences West to get large buckets of ice every morning to bring back to our laboratory so we could have some ice in which to store our specimens. We had a small preparative centrifuge that we got on our grant, but we desperately needed an ultracentrifuge, but I didn't have the money. But people in Health Sciences East, Leon Levintow and Mike Bishop, were very gracious and I could use their ultracentrifuges. But still, it meant walking a couple hundred yards quite a few times during the day. It was extremely difficult to carry out research.

So eventually, I got some funding to install a cold room in one of my labs, so there goes your laboratory space, but we needed the cold room. I got some equipment, but the laboratories were up and down the hall. It was okay; we functioned. But things were not as easy or efficient as they could have been.

Hughes: How had the shift to the basic sciences occurred? As you well know, UCSF was not historically a research institution.

Boyer: I don't know. Holly Smith would be someone who probably has the best sense of that; he was there for that time. As I understand it, in an attempt to revitalize the medical school, they brought in several people. They brought in Holly Smith from Harvard as chairman of the Department of Medicine; Bert Dunphy, Department of Surgery; Julius Comroe was director of the Cardiovascular Research Institute. I think Comroe and one of his associates, Isidore Edelman, were very instrumental in first getting a couple of good clinical guys in there, and then in turn they realized the need to also get the basic sciences going. So I think that was the germination of that move.[1]

## Colleagues in the Department of Microbiology

Boyer: When I was recruited, there was one sympathetic faculty member, Leon Levintow, who just retired this last year. Leon had retired from NIH [National Institutes of Health] and took a position here. He had a background in animal virology and tissue culture work. He ended up

---

[1]See the UCSF Campus Oral History Program's interviews with Isidore Edelman, Richard J. Havel, Clark Kerr, and Lloyd "Holly" Smith for a variety of accounts of the mid-1960s transformation of the UCSF campus on Parnassus Avenue.

recruiting Mike Bishop who in turn brought Harold Varmus. Warren Levinson was also newly recruited at the time. He was working on Rous sarcoma virus.

When I got here, Levintow and Warren Levinson and Joel Goodman were here in the Department of Microbiology. There was one person in biochemistry who had a background in molecular biology, Jim Ofengand. But when I got to UCSF, there wasn't a hotbed of scientific excitement. It was extremely frustrating to not have a sympathetic ear. Leon was very kind and helpful, but he wasn't that interested in what I was doing, from what I could perceive. But he really was very helpful.

Hughes: Dr. Jawetz was a pretty classical microbiologist?

Boyer: Yes, he was a classical microbiologist.

Hughes: Was he sympathetic to what you were doing?

Boyer: No. I liked Ernie, although we had our differences, and got into some disputes over a number of things. I never felt that Ernie was particularly helpful. He did not try to provide me with any help so far as my research went. He just never was interested.

Hughes: Why did he recruit you?

Boyer: I think he was mandated to do so. He was just doing what he had to do.

Hughes: So you had trouble getting support for the things that you needed?

Boyer: Yes. He pointed out some funds that could be available, but I never had the impression that he was supportive or even particularly wanted me there.

Hughes: Well, the other people that were more interested in the molecular aspects, Bishop and Varmus and Levintow and Levinson and Ofengand--

Boyer: Bishop came about a year or two after I did [1968]. Within a year, I was looking at other positions. I was very dissatisfied with things and felt that there were other places where I might have more stimulation and support. But the lack of a core of hard basic science at UCSF necessitated me to go to Berkeley a lot, to talk to people, to hear seminars, because we just didn't have a good seminar program. I went to Stanford occasionally to hear seminars there and talk to people.

But when Mike came, he provided some scientific stimulation. Mike and I worked pretty hard in those days. We'd be there in the evenings, on the weekends. He was just good company.

Hughes: Were you the only two working late into the night?

Boyer: These are the two I remember. There weren't many others that had the same sort of crazy work habits we had.

## The Department of Biochemistry

### William Rutter and Gordon Tomkins

Hughes: Of course, Dr. Rutter hadn't yet come, so there was not much happening in biochemistry?[1]

Boyer: No. And as a matter of fact, that was very frustrating. Of course, being an assistant professor, I was not privy to any of the things going on, other than I knew the fact that they were looking for a chairman of the department, and I knew they were having trouble. I did talk to some of the candidates, went out to dinner with them with a larger group of people. Earl Stadtman looked at the job, and Sol Spiegelman--those are the two I can remember at the moment, but there were a series of candidates--and Gordon Tomkins came through. I was just so terribly disappointed when Gordon turned down the job, because he was so exciting and supportive and stimulating.

Hughes: Is that why people here talk so much about him?

---

[1]After a long recruitment effort (1962-1969) for a new chair of Biochemistry, conducted by UCSF faculty committed to advancing the basic sciences, Dr. William Rutter agreed to come to San Francisco to chair the department in 1969. The department was renamed Biochemistry and Biophysics in autumn of 1968 at Dr. Rutter's request, (Dean's Office Records, AR 90-56, UCSF Library). For details of the recruitment, see William J. Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco," an oral history conducted in 1992 by Sally Smith Hughes, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2001.

Boyer: Yes, probably.

Hughes: Ideas flowing all the time?

Boyer: Yes, his ideas and his eclectic interests. He could just talk to anybody about their research, and if not genuine, at least express an interest, but I think it was very genuine. I would go talk to him, and he would get all excited and say, "Gee, this is great," and we talked about a lot of different things and possibilities and directions of research. Nobody else did that. There was nobody else around that really got enthusiastic about what we were doing.

Hughes: Why did he turn the job down?

Boyer: I think I've heard Gordon say he didn't want to take on a management role. His strength was not in organizing and being political, which took a lot of savvy and insight to the politics of the university and that institution [UCSF]. It was so important to be politically savvy and to succeed, at least to run a department or build a department. So Gordon turned down the chairmanship.

Then Bill came and looked at the chairmanship, and we got all excited about Bill, and Bill turned it down. Then he called back and said he had thought about it some more, and he said yeah, he wanted to do it. He had talked Gordon into coming. That was a big turnaround. That was a big change.[1]

Hughes: Had he known Dr. Tomkins?

Boyer: I'm sure he did, yes.

---

[1]Although Gordon Tomkins turned down the proffered chairmanship of the Department of Biochemistry in the mid 1960s, he agreed to come in 1969 as vice chair. Dr. Isidore Edelman recalls his attempt to get both men to "recruit" each other by hosting a get-together in his San Francisco home. See "Interview with Isidore Edelman" (San Francisco: UCSF Campus Oral History Program, UCSF Library, forthcoming), p. 48.

Hughes: How did they work as a team?

Boyer: Well, I don't recall much about it. It seems to me that they had a lot of mutual respect, and I think they worked well together. I think Bill was very much aware of the effect that Gordon had on younger scientists and with his own peers. His reputation was stellar. He knew everybody. He was very knowledgeable about all areas of science, so he was the perfect guy to come in and provide some sort of broad support for the department and the school.

Hughes: Well, what convinced you to stay?

Boyer: Things got better. Research went well. There were more people to talk to. But I continued to be unhappy. The space was very confining and constricting, and I felt I deserved better, and I wasn't being recognized. I had opportunities to go elsewhere, but the disruption and facing a new set of problems wherever you go, and leaving California--

Hughes: Were you also beginning to see that things might change for the better at UCSF?

Boyer: Yes. Oh, absolutely. Once Rutter started to develop the Department of Biochemistry and Biophysics, it was a much different place.

## Boyer's Associations with the Department of Biochemistry

Hughes: Did you have a lot of interchange with Biochemistry prior to 1975 when you actually joined the department?[1]

Boyer: Oh, yes.

Hughes: So you were attending seminars--

Boyer: Oh, yes.

---

[1]In December 1975, Boyer left the Department of Microbiology to become associate professor of biochemistry in the Department of Biochemistry and Biophysics.

Boyer: In fact, one of Bill's earliest recruits, Howard Goodman, came [in 1970 as assistant professor] and we had a common interest. We started a collaboration, which was extremely productive, when Howard came to the department. Howard and I spent a lot of time thinking about common things. We worked together in each other's labs. We'd be working at night and on the weekends together, interacting with the other people. It got to be a very exciting place in the early seventies for me.

## The Division of Genetics

[Interview 2: March 28, 1994] ##

Hughes: I asked you off-tape, Dr. Boyer, if you knew about the rationale behind the formation of the Division of Genetics in the Department of Biochemistry in 1975.[1]

Boyer: I did know at one time, but I just can't recall the circumstances around which the division was formed. There were a number of geneticists on campus, and they had an interest in putting together a Division of Genetics, I think for graduate student purposes, and being able to grant a degree in genetics. Charlie Epstein was there, and people in biochemistry and microbiology. There were people in different departments with an interest in genetics.

Hughes: Were there others in the Division of Genetics?

Boyer: There were others involved. I think we had maybe two or three appointments in that division. I know Charlie Epstein was very much involved. And [in 1978] we hired Tom Kornberg and John Sedat. I

---

[1]From 1976 through 1981 Dr. Boyer was Director of the Graduate Program in Genetics. William J. Rutter, "Report On The Department Annual Report 1975," Department of Biochemistry and Biophysics, (UCSF, May 1976). By 1985 Genetics was an interdepartmental graduate program that was included in the Program in Biological Sciences, funded by a $13 million grant from the Lucille P. Markey Charitable Trust. Papers relating to the genetics program are found in Dean's Office Records, AR 90-56, UCSF Library.

don't know who else had affiliation with the division in the early days.

Hughes: Which implies that you weren't having a lot of interaction with whoever else was in the division?

Boyer: No. It didn't have a formal structure to it all that much. We had a part-time secretary. To tell you the truth, I think it was just an ancillary component of the biochemistry department, which had some semblance of autonomy. But it really wasn't autonomous; it was still very much under the control of the biochemistry department and Bill. I think he wanted the division to be in biochemistry rather than in another department so that he could try to maintain the quality of the basic science. I don't think he had any Machiavellian aspirations regarding that particular division or the space. I think it was just a genuine concern on his part that we continue to have good scientists around, and the best way to do that would be to have the division under the umbrella of the biochemistry and biophysics department. That's a bit of speculation; I can't say for sure.

## Boyer Joins the Department of Biochemistry, 1975

Hughes: I thought maybe the division was set up to lure you into the department.

Boyer: No, I don't believe so. I don't know of any overt luring [laughter] on the biochemistry department's part. I just had a sort of dissatisfaction with microbiology, and saw this Division of Genetics, which included new space in the Health Sciences East Building, as an opportunity to get some new and more efficient lab space. I had always had a certain resentment about the fact that I didn't get the space I was promised when I went to UC. I mentioned that in my talk.[1] I threw in a little jab there. [laughter] But that was one of the reasons I was interested in going to the Department of Biochemistry.

Hughes: Do you remember who approached whom about the move?

---

[1]At the time this interview was conducted, Dr. Boyer had recently given a presentation at the symposium for William J. Rutter's retirement, "The Beginning of Biotechnology. The New Biology: A Symposium in Honor of William J. Rutter and His Scientific Contributions During a Quarter of a Century at UCSF," 18-19 March 1994, UCSF.

Boyer: I think I approached Bill Rutter. I don't think there was any overt move on their part to do it. Why should Biochemistry use up its space for somebody who was already there, when Bill could have hired another person?

Hughes: But he did, so Biochemistry must have found you of some advantage.

Boyer: Yeah, I suppose. I guess at the time that I switched over to Biochemistry, I was fairly in the forefront of all the recombinant stuff, and I was still teaching a lot of people how to do it. I had a lot of people coming through my labs, and I provided a lot of help--well, not a lot of help--but help for other people around campus. So I had a certain visibility.

Hughes: What difference did it make to be in the biochemistry and biophysics department, other than the fact that you now had space in HSE?

Boyer: I probably had more interaction with people in Biochemistry from a scientific point of view.

Hughes: Was that a matter of proximity? Although you weren't really very proximate, were you?

Boyer: No. It had nothing to do with proximity. But I never felt I had support from Microbiology.

Hughes: I know that you had been collaborating with Howard Goodman.

Boyer: Yes.

Hughes: Did it make any difference to the collaboration that you were now within the department?

Boyer: No, I don't think it changed anything, other than the fact that, from my perspective, I got into some new lab space, and had more lab space. It was a better situation for my own laboratory.

Hughes: Did you have access to greater resources?

Boyer: I'm not sure what you mean by resources.

Hughes: When you needed equipment, for example, were there certain things that the department itself would provide?

Boyer: No, I don't think there was any advantages with respect to equipment. Whatever collegiality existed, existed beyond departmental lines, and you could use equipment if you needed it. Of course, it all depended on how much it was being used by the person you borrowed it from or imposed upon.

Hughes: I went over to talk with Mary Betlach, your former technician, who said that Dr. Jawetz had an ultracentrifuge.[1] Am I right?

Boyer: No, it was just a preparative centrifuge.

Hughes: He would not allow anybody in your group to use it, except very occasionally.

Boyer: Yes. Except we used to sneak in after five o'clock, after everybody was gone, and use it surreptitiously. [laughter] Well, the differences were a question of style. I had great admiration for Ernie Jawetz. We didn't quite hit it off around the laboratory, because we were continually bumping into each other. He wasn't terribly sympathetic towards my needs in terms of doing research.

Hughes: Was that largely because he was a classical microbiologist and you were thinking molecularly?

Boyer: I have no idea. It was just a clash of styles.

## Collegiality in Biochemistry

Hughes: In 1975, the year that you arrived in Biochemistry, the first annual research meeting of the department occurred at Asilomar.[2] Did you go?

---

[1]See oral history of Mary Betlach, Ph.D., interviews conducted in 1994 by Sally Smith Hughes, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, in process. Betlach was a technician in Boyer's lab from 1972-1993 and in the late 1970s was involved with recombinant DNA and plasmid development. She later earned a doctorate in biochemistry/molecular biology at UCSF.

[2]William J. Rutter, "Report on the Department, 1975," Department of Biochemistry and Biophysics Annual Report, 1975.

Boyer: I'm not sure whether I was a member of the department or not at that time [October 1975].

Hughes: According to the annual report, you didn't officially make the transfer until December of 1975. But there probably had been some prior negotiations.

Boyer: No, there weren't any negotiations. The whole thing depended on when the lab space was finished. I believe that the Asilomar meeting was in the fall of '75. Do you know the dates?

Hughes: Was it usually in the fall?

Boyer: Yes, when the new graduate students arrived.

I have the impression that there was a meeting actually very close to where we are at the moment [Mill Valley, California], at the Ralston Retreat. I recall being at this Ralston Retreat with the Biochemistry faculty. I can't remember whether I was a member of the faculty then or just proposed, or unofficially a part of it. But we met right down below us. It was a small group; it was just the full-time faculty. I have the impression that the retreat was what gave us the idea for doing Asilomar, that we should have a larger meeting. That could be totally wrong, but that's what I think.

The first Asilomar meeting,[1] and subsequent ones, were to familiarize students, postdocs, and the faculty with each other, with the work they were doing, to promote interaction, get to know each other socially, I guess. Faculty members from other departments were invited to come and talk about what they were doing as well. It was a two, two-and-a-half-day meeting.

Hughes: What was the atmosphere?

Boyer: The first couple were very good, as far as I remember--a lot of interactions. I just remember them being very good. Later on, they got to be overwhelming because of the numbers involved. They got

---

[1]The departmental meetings were held at Asilomar, a Pacific Grove, California conference site frequently used for University of California retreats. These should not be confused with the Asilomar conferences (Asilomar I in January 1973, and Asilomar II in February 1975) that dealt with the potential hazards of biological research.

too long and, after a point, I didn't go every year. It got to be a show-and-tell type of atmosphere, and I didn't particularly care for that. So I didn't go.

Hughes: Well, another institution that I read about is the Chelsea Pub. You may think these are strange questions on my part, but it's of great interest where scientists meet to discuss science, even in the most casual of circumstances. Was the pub indeed a fixture of life?

Boyer: It was for a period of time, but I think it was more a fixture for the postdocs and graduate students. Occasionally faculty would be there.

Hughes: You didn't go very often?

Boyer: I can remember being there a number of times. I don't remember anything very significant being discussed, but I'm sure there was. [laughing] Probably too many drinks. But it was a place to unwind, and a lot of times people would go later in the evening, if they'd been working in the lab, and just hang out there a little bit.

Hughes: This pattern started in the Department of Microbiology?

Boyer: Not to my knowledge. I can't remember doing that then.

Hughes: It was a Biochemistry custom.

Boyer: I think so, yes.

## Recombinant DNA Research

### Splicing Plasmids, 1972-1973

Hughes: I think the best way of starting to discuss your research would be to describe what led up to the recombinant DNA research reported in the 1973 paper in the *Proceedings of the National Academy of Sciences.* What had to have been established before you could do that work?

Boyer: There were two papers, one in '73 and one in '74.[1] I don't think you want to discuss one without the other. Bob Helling was a fellow graduate student of mine at the University of Pittsburgh. He came out to my lab on a sabbatical. I think this was summer of '72, and this was when Stan Cohen and I actually got together. I was interested in doing in vitro recombination of DNA, and I had been for some time, realizing that restriction enzymes would be important for that. We had been working with restriction enzymes for a number of years.

Bob and I, as part of his sabbatical, were trying to do in vitro recombination with a lambda fragment and a plasmid that was called lambda DV Gal. It was a plasmid derived from a bacteriophage, lambda, which had a beta-galactosidase gene in it. We were trying to use that as a plasmid vector, recombining that with another piece of DNA. We were not getting anywhere.

We didn't have good assays yet for monitoring restriction digests with ethidium bromide staining. We were doing gel electrophoresis, but we were still using radioactive labels. It was a very tedious procedure. We were not getting anywhere. As it turned out later, the *Eco* R1 site in lambda DV Gal disrupted the origin of replication. We didn't know that at the time.

## Stanley N. Cohen and the Plasmid Meeting in Hawaii, 1972

Boyer: So Bob and I had been working on that that summer [1972], and I had been working with Stan Falkow. I had known Stan for some time, and got together with him and Stan Cohen.[2] Stan Falkow introduced me to Stan Cohen.

Hughes: Is this the deli meeting in Waikiki in November 1972?

Boyer: No. This was prior to that. We were just discussing our interests. They told me about the upcoming meeting in Hawaii. It was a Japan-US meeting to be held in Hawaii [in November 1972].

Hughes: On plasmids?

---

[1]S. N. Cohen, A. C. Y. Chang, H. W. Boyer, and R. B. Helling, "Construction of Biologically Functional Bacterial Plasmids *In Vitro*," *Proceedings of the National Academy of Sciences of the United States of America* 70, no. 11 (1973): 3240-44, and J. F. Morrow, S. N. Cohen, A. C. Y. Chang, H. W. Boyer, H. M. Goodman, and R. B. Helling, "Replication and Transcription of Eukaryotic DNA in *Escherichia coli*," *Proceedings of the National Academy of Sciences of the United States of America* 71, no. 5 (1974): 1743-47.

[2]For Cohen's perspective on the meeting and many other topics see the oral history of Stanley N. Cohen, interviews begun in 1995 by Sally Smith Hughes, ROHO, The Bancroft Library, University of California, Berkeley, in process.

Boyer: On bacterial plasmids, yes. And since we had just done some work on two restriction and modification enzymes controlled by plasmids, they felt that we should come and talk about that.

Hughes: It wasn't a meeting that you routinely went to?

Boyer: Well, this, I think, was the first one ever held. Japan had a large interest in plasmids. They had a lot of scientists working on plasmids because they had a major problem with bacterial resistance to antibiotics, and these were all caused by plasmids.

Hughes: More problems than elsewhere?

Boyer: It was very prevalent there. I don't know whether it was ever monitored that carefully elsewhere, but apparently Japan was not so judicious in its medical use of antibiotics, as I understood it, which would have promoted resistance. More indiscriminate use of antibiotics would lead to accumulation of the resistant organism.

## Research Prior to the Boyer-Cohen Collaboration

Boyer: So we went off to Hawaii. We had done sequence work on the site cleaved by the enzyme.[1] We knew from the work of Ron Davis and Janet Mertz, who worked in Paul Berg's lab at Stanford. We had given some of our *Eco* R1 enzyme to Paul Berg. He gave some to those people. They had shown physically that when the R1 enzyme cleaved DNA, that the ends would reanneal, that they were what we call sticky ends.

And this was the same time that we determined the sequence of the cleavage site, so we could tell from the sequence of the termini that we would have short sticky ends of four overlapping base pairs. The thing that was somewhat interesting at the time was that we knew that cohesive ends existed naturally in bacterial viruses, like lambda, had twelve overlapping reannealable nucleotides, and that these were stable at room temperature. But it was somewhat surprising, at least to me, that reannealing would occur so efficiently with just four nucleotides involved, albeit at slightly lower temperatures.

Hughes: Why were you surprised? Because of the lower number?

---

[1]J. Hedgpeth, H. M. Goodman, and H. W. Boyer, "DNA Nucleotide Sequence Restricted by the R1 Endonuclease," *Proceedings of the National Academy of Sciences of the United States of America* 69, no. 11 (1972): 3448-52.

Boyer: Lower number and the lower energetics involved; it just wouldn't be stable. But probably what's happening is that even at room temperature, there would be a lot of these forming, but they were thermodynamically unstable; they wouldn't stay annealed; they were in a constant state of flux, of closing and opening, closing and opening. If you could add another enzyme, DNA ligase, then you could catch the reannealed configuration in a protein-DNA complex and re-ligate the bonds and then they would be stable.

As it turns out, you can take these fragments of DNA with R1 ends and transform them into a bacterium, and the enzyme in the bacterium will actually reseal them. As a matter of fact, when we published our first paper, we found that you didn't have to treat it with ligase. You could recover recombinants just by mixing the fragments and taking them up into the bacteria without treatment with the ligase.

So we had the preliminary information available when we went off to Hawaii. We heard Stan Cohen at that time describe a small plasmid that he had been working on called pSC101. It carried the gene for resistance to one antibiotic, tetracycline. He talked about a number of other, larger plasmids that had a number of drug resistance markers on them.

Hughes: Which he also had developed?

Boyer: He had characterized them. Stanley thought he had developed the pSC101 from a larger plasmid, but people at the time thought that he had just isolated a natural one in the course of his experiments.

So in any case, since it had one antibiotic marker on it, and the fact that it was so small, it could be transformed into bacteria. This seemed to be a very interesting plasmid to see if it could be cleaved by the *Eco* R1 enzyme, and also to look at the structure of other plasmids by treating with the R1 enzyme.

Boyer: At that same meeting [in Hawaii], I tried to talk Stan Falkow into collaborating on trying to dissect various bacterial plasmids, and he wasn't too interested. He was more interested in the medical end of things, so he suggested that Stan Cohen and I get together and do this. So Stan and I set up the collaboration, that we'd first look at cleavage

patterns, and then we'd try to do the in vitro recombination of those various fragments of plasmid.[1]

##

Boyer: In general terms, I think we knew how significant this work would be. It became more apparent as we were doing experiments. But I do believe I had a fairly good handle on it. I didn't realize the wide-range impact, that it would be very significant if one could do that.

Hughes: Were you thinking only scientifically, or were other applications coming to mind?

Boyer: I think it was primarily scientific.

Hughes: You weren't thinking--

Boyer: Well, I want to set the stage here, because we were just talking about recombining bacteria and viruses and bacterial plasmids and bacterial chromosomes. That's what our focus was there, and we didn't even know if we could do it.

## Technical Breakthrough: Characterizing DNA Fragments

Boyer: We came back from that meeting and, before we got started on the collaboration, I went to Cold Spring Harbor, where Joe Sambrook and Phil Sharp showed me the staining of DNA fragments that they had been separating in a gel based on size and had stained with ethidium bromide.[2]

---

[1]See Appendices B and C for a cartoon representing the Waikiki deli meeting and a diagram of the molecular cloning procedure.

[2] The use of ethidium bromide stain combined with agarose gel electrophoresis is described in P. A. Sharp, B. Sugden, and J. Sambrook, "Detection of Two Restriction Endonuclease Activities in *Haemophilus parainfluenzae* Using Analytical Agarose-Ethidium Bromide Electrophoresis," *Biochemistry* 12 (1973): 3055-63.

It was such a breakthrough in terms of how fast we could move. If we had to do this research with the techniques prior to that, it would have just taken forever. When I saw those gels back in Cold Spring Harbor, I was just so excited I couldn't wait to get home, get back to the laboratory.

When I came back, I told Bob Helling about it, and suggested that he work out the variables and the parameters involved in looking at the separation of fragments on gels based on size, and the various staining approaches. So he did a lot of work on that and did a wonderful job. We could show that there was a relationship between the size of the fragments and their mobilities in the gels, and they could be stained in a couple of minutes. You could see the results from your experiments in a couple of hours, and you could essentially do endless experiments.

Hughes: What had you had to do before?

Boyer: Prior to that, we primarily did ultracentrifugation analysis of cleaved DNA, in which the resolution was terrible. We had to fractionate sucrose gradients. We would do something like five- to six-hour ultracentrifugation runs, and then you had to remove the tubes. You punctured the bottom of the tube with a needle and you collected drops on little pieces of paper. You'd get about fifty pieces of paper per tube. Then you would dry those, put them in scintillation vials with scintillation fluid, and count them in the scintillation counter. Then you'd have to count each one for two to three minutes. This is using radioactively labeled DNA, so you had to prepare radioactive DNA, which was a mess. You had to be careful. No matter how careful you were, you always had accidents; you'd get stuff on the floor.

Hughes: What was the radioisotope?

Boyer: We would use tritiated thymidine and some $P_{32}$ phosphorus, $P_{32}$-labeled DNA. So it was just a terrible job preparing that stuff. It was valuable substrate, and you hated to use it up, and every time you goofed up an experiment, you'd be so depressed, because you'd wasted all this time and effort and money. But with the gel electrophoresis and the ethidium bromide stain, you didn't have to make, for all intents and purposes, radioactively labeled DNA. You could just take DNA and it was so much easier.

## Boyer and Cohen Collaborate on Prokaryotic and Eukaryotic DNA Exeriments

Boyer: So once we got a handle on that, which didn't take too long, we did the experiments with Stan's lab, in which we took a couple of plasmids that he had. The pSC101 plasmid we could cleave was cut one time by the R1 endonuclease. We could cut up other plasmids with the enzyme, and essentially cut out fragments which had the R1 termini, and some of these fragments would contain antibiotic-resistant genes. So we could recombine them in a test tube and transform the bacterium, select for various antibiotic resistance markers, and take the bacteria that carried these various combinations of markers. We could purify the plasmids from those strains, cut the plasmid DNA with the R1 enzyme again, and then run those plasmids in gel electrophoresis alongside the original ones that were cut with the same enzyme.

Well, what we didn't know is whether or not we could do the same thing with eukaryotic DNA. Let me point out that what we were able to do in this bacterial plasmid work was simplified somewhat because we could select for recombinant plasmids through antibiotic resistance of transformed *E. coli*.

We could show identity between the fragments, and then show for the first time that there were certain fragments of plasmid that contained the antibiotic resistant marker. So that was the first paper. But at that time, we knew you could do in vitro recombination, we could transform bacteria, and we could recover the in vitro recombined plasmids.

Now, the number of recombinants that you got was a fraction of what you'd get if you did not cleave the DNA. As a matter of fact, there were several logs difference, if I can recall. And so you <u>were</u> looking for a fairly rare event. It wasn't out of the question, but it was somewhat rare. But if you didn't have the ability to select for those genes, it would have been a nightmare, and nobody would have done it in the first place.

The next question we asked was whether we could do the same thing with eukaryotic DNA. Could we put eukaryotic DNA into bacteria? And would it replicate? And could we recover recombinant plasmids

with eukaryotic DNA if we had no way to select for the recombinant event? There's a subtlety there I don't think a lot of people appreciated at the time. Once you could do it, it was great, and nobody thought of how much time we worried about that. And we actually did some subsequent experiments to maximize the efficiency of recombination.

Hughes: Is it pertinent to go into how you did increase the efficiency?

Boyer: No, I don't think it's terribly relevant. We spent a great deal of time looking at the parameters. You look at the ratio of the ends of the fragments of DNA, the concentration, and how long the DNA molecule is. You could have done this experiment the wrong way. We didn't know ahead of time; we just sort of assumed that we could force it in one direction, just on general principles. But if you take a very short DNA molecule, it can find its own end and form a circle very easily. And the shorter it is, the more easily it can find its end.

So you can effectively calculate the concentration of the ends of a molecule relative to itself. So if you had a short molecule that you wanted to recombine with a fairly large plasmid, and you didn't have an excess of these small ones relative to the large one, they would all close on themselves, and the recombinant event would be rare.

Hughes: Is this in retrospect?

Boyer: This was after the initial experiments, and we published a paper on that. There was a formula describing that. It all had to do with the flexibility of DNA. At some point, when a molecule gets too short, it can't bend enough to find its own end.

## The Biohazards Problem

Boyer: At that time, we were facing up to a general awareness in the scientific community about the "hazards" of this type of research. People were concerned that maybe we would put the wrong kind of gene into a bacterium if we tried using eukaryotic DNA. In particular, if we carried out recombination between a bacterial plasmid and an animal virus that caused cancers in various laboratory animals, they worried that we might end up with a sewer full of bacteria carrying genes that would cause cancer, and that sort of thing.

Hughes: Was this a concern before you had done the *Xenopus* work?

Boyer: Yes. There was a general awareness about that, if I remember correctly. We obviously hadn't had the Asilomar conference on recombinant DNA yet, but there was some awareness. I can remember years before we'd had a little discussion at an European Molecular Biology Organization (EMBO) meeting in Europe regarding using molecular genetics and so on and so forth in biological warfare experiments. So the thing was floating around.

And also, the other thing that was very evident, there was concern in the scientific community because of large-scale production (these are all relative terms) by laboratories of large amounts of SV40 and polyoma viruses. This was something that actually came out of the focus that Cold Spring Harbor Laboratory took on viruses such as SV40, polyoma, and the adenoviruses. There was a concern and outcry by a number of people at that time; I can't remember who.[1]

Hughes: There actually was an Asilomar conference on that very subject in early '73.[2]

Boyer: Yes. Out of that came a book which was called *Biohazards in Biological Research*, which was published by Cold Spring Harbor Press actually.[3] Jim Watson took a very cautious, even negative, position on doing research with these elements, if I remember correctly. In contrast, he did a big turnaround by the time recombinant DNA work came along. Probably out of having just thought about it more, and having some experience behind him, I think he changed his position.

But nevertheless, there was a major problem. We didn't want to work with an animal virus for those reasons.

---

[1]For a detailed account of these events, see Sheldon Krimsky, *Genetic Alchemy: The Social History of the Recombinant DNA Controversy* (Cambridge: MIT Press, 1985).

[2]The first Asilomar conference, held January 22-24, 1973 (also called Asilomar I) dealt with the general biohazards of biological (viral) research. Asilomar II held on February 24-27, 1975, provided the philosophical and practical basis for the development of NIH guidelines for recombinant DNA research. For the views of the scientist who organized Asilomar I and II, see Paul Berg, Ph.D., "A Stanford Professor's Career in Biochemistry, Science Politics, and the Biotechnology Industry," an oral history conducted in 1997 by Sally Smith Hughes, ROHO, The Bancroft Library, 2000.

[3]The full citation is, A. Hellman, M. Oxman, and R. Pollack, eds., *Biohazards in Biological Research: Proceedings of a Conference on Biohazards in Cancer Research at the Asilomar Conference Center, Pacific Grove, California, 22-24 January 1973* (New York: Cold Spring Harbor Laboratory, 1973).

## Cloning Successes

Boyer: For the next set of experiments, what we really needed was a small, well-defined piece of eukaryotic DNA that we could characterize and with which we could show without going through massive amount of efforts that we had actually cloned a piece of eukaryotic DNA. Animal viruses were well characterized because they could be purified and were small, and you could characterize the DNA with a restriction enzyme.

Let's say you took total mouse DNA, and you tried to carry out the cloning experiments. Let's say you got some recombinants and you looked at them. Then you had to go through a fairly rigorous procedure, at least at that time, to identify that as a piece of the mouse chromosomal DNA. So we were looking for something that was well defined.

The problem was in those days, before you could do the in vitro recombination and cloning thing, there wasn't that much around. You had the animal viruses. There was some work being done with mitochondrial DNA, but it was a fairly large piece of DNA. I was at a Gordon conference [June 1973] where I described the work that Stan and I had done with the bacterial plasmids. There was a graduate student there from Paul Berg's lab, John Morrow. I was talking to John, and I said, "Well, the next thing to do is, we've got to recombine a piece of eukaryotic DNA to the plasmid, and show that it can replicate," and blah blah blah. "And we're looking for the right--"

He says, "Oh, I have some amplified ribosomal DNA from *Xenopus laevis*," that he had gotten from Don Brown. With the enzyme we had given to Paul Berg, John had shown that this DNA could be cleaved by the R1 enzyme. So it looked like that might be a <u>good</u> source of eukaryotic DNA that we could recombine into plasmids.

So John checked with Don Brown and asked him if it would be okay if we could use that. So John said, "Well, I'll just give you some of that DNA." I said, "No, no, I'd be happy to put you on the paper if you gave us the DNA." So he gave us some DNA, and what we showed is that you could cleave this amplified toad DNA into a

couple of different pieces of DNA. So we then took that and recombined it with the plasmid.

The big question was, how could we recover it? We could cleave the bacterial plasmid, which carried a tetracycline resistant gene; we could cleave the ribosomal DNA, and we could mix them together in a test tube. They could be treated with DNA polynucleotide ligase. They could be transferred into *E. coli*, and then once you transformed the bacterium, you could select for tetracycline resistance. And that's what you had.

Then you had to take all those colonies that were resistant to tetracycline and remove plasmid from them. Then the question was, how frequently could you recover a plasmid with a piece of the eukaryotic DNA in it? And we could tell that by purifying the plasmid, cutting it with the enzyme and running it on gels, and comparing them with the original reactants or fragments of DNA that we put into it.

So it turned out that we were able to recover at a fairly reasonable frequency. I can't remember exactly what it was--maybe 10 to 30 percent of the transformants carried recombinant DNA.

Hughes: How did this compare with the bacterial system?

Boyer: Well, in the bacterial system, the comparison of several different orders of magnitude difference in frequency was relative to the uncut plasmid. If you compared those two transformations, we had a fairly significant recovery. Anyhow, it didn't take us long to find a half a dozen or more of these recombinant plasmids, and we just characterized them and showed that they contained the fragments that we had started with. Then we showed that you could actually make the ribosomal RNA in the bacterium, and that it would hybridize to the *Xenopus* ribosomal DNA. So that was a little bit of icing on the cake that confirmed that we had cloned eukaryotic ribosomal DNA.

Hughes: You're telling this very soberly. Was it pretty exciting at the time?

Boyer: Oh, yes. Actually, I think the most exciting moment was when we did the first experiments with the recombined plasmid DNA. Bob

Helling and I looked at the first gels, and I can remember tears coming into my eyes, it was so nice. I mean, there it was. You could visualize your results in physical terms, and after that, we knew we could do a lot of things. There were some unanswered questions, but I think that was the key. That was the key.

The frequency of recombination was one thing, the fact that we could recover it, and secondly, we went on to spend some time on this, to show that eukaryotic DNA in a bacterium, when it did replicate, replicated very faithfully. There are some types of DNA that, because of their structure, don't do that, but those are very rare.

Hughes: How did you show that it indeed did replicate faithfully?

Boyer: This was done in some subsequent work. I don't think a lot of people questioned that seriously. I think a few people did, and we did. Because if you had a piece of eukaryotic DNA that replicated in a bacterium, unless it replicated faithfully, you didn't have much.

Hughes: [laughs] That's right.

Boyer: We had a postdoc who came from Cal Tech--Wes Brown, who went on to work with Alan Wilson at UCB (molecular clock). He'd been in Jerry Vinograd's lab there at Cal Tech, and he had worked on the electron microscopy of rat mitochondrial DNA. So we cloned fragments of rat mitochondrial DNA in bacteria, and grew them. We would grow cultures for long periods of time, and subculture, subculture, subculture. After many generations of replication, you can ask then by reannealing the cloned mitochondrial DNA with bona fide rat mitochondrial DNA if there are a lot of irregularities in the reannealed DNA. We essentially could pick up any differences after many, many generations. Of course, this is a real key for anything in genetically engineered biopharmaceuticals.

## Considering Commercial Applications

Hughes: Were you beginning to think that this technology might have commercial applications?

Boyer: Yes.

Hughes: Is the *Xenopus* work what really prompted thinking in commercial terms?

Boyer: Yes, I think we were thinking about it at that time. Not in any grandiose ways, but sitting around the laboratory talking about, "Well, now if you can clone eukaryotic DNA, you can clone the gene for human insulin or human growth hormone or whatever you can think of, and you should be able to make it in a bacterium."

Problem was, we didn't know how to isolate those genes. If you just randomly isolate the pieces of DNA from any organism, how do you know what you have? You have to do a lot of analysis, or you'd have to have some way of identifying the gene that you wanted.

There was a lot of subsequent work by other laboratories which allowed you to do that. One was that people were able, around the same time, to purify, to a certain extent, messenger RNAs. If you had the right assay, you could take RNA from a particular tissue, let's say pancreas or liver or what have you. By using in vitro translation of the message with, let's say, a radioimmunoassay for a particular protein, you could purify with those techniques, or at least enrich a messenger RNA population for a particular protein. So if you had that messenger RNA, you could then make a cDNA [complementary DNA] copy and clone that, and characterize the resultant clones and ask if they actually did have the sequence for that particular DNA. So that was an approach used.

The other approach was just to reverse that, which would be to clone the genomic DNA, large numbers, and then use your enriched messenger RNA, have it radioactively labeled, and then look for colonies or clones of DNA that would hybridize with your particular messenger RNA. So those were some of the things around. In those days, purifying messenger RNAs was a tough job.

## The Research Moratorium

##

### The Singer-Soll and Berg Letters

Boyer: If I remember correctly we published this work on *Xenopus* in '74.[1] I presented that at a Gordon Conference on Nucleic Acids that year,

---

[1]J. F. Morrow, S. N. Cohen, A. C. Y. Chang, H. W. Boyer, H. M. Goodman, and R. B. Helling, "Replication and Transcription of Eukaryotic DNA in *Escherichia coli*," *Proceedings of the National Academy of Sciences of the United States of America* 71, no. 5 (1974): 1743-47.

which was the year after the other one I referred to when I talked to John Morrow.

Boyer: At that conference, there was a letter drafted by a few scientists which I signed; I had mixed feelings about it.[1] There's a footnote in the paper that Stan and I wrote suggesting that people should think cautiously about cloning eukaryotic DNA at random, and so on and so forth.

Hughes: Is that really in there? I read that you had at first wanted a cautionary footnote, but you took it out.[2] I've got the source. [tape interruption while Boyer reads the document.]

Boyer: Yes. I didn't remember correctly. We were thinking about putting a little note in there, but decided not to do it.

Hughes: Do you remember why?

Boyer: I didn't think it was appropriate for a scientific paper, for a few scientists to come to any judgment. I didn't feel qualified to do it. I mean, why create a controversy when one didn't exist at the time? But convening the Asilomar conference I think came out of the original letter from the Gordon conference.

Hughes: Let's talk about the Gordon conference, where you first discussed your work on recombinant DNA. The Gordon conference was in June 1973, and the first paper on your recombinant research did not come out until November. The way I read it, you presented the material, and it fell somewhat flat until somebody later in the session commented, saying something to the effect, "Well, now we can splice just about any DNA." As a result of that realization, Maxine Singer added a half-hour discussion at the end of the Gordon conference on

---

[1]Dr. Boyer refers to the so-called Singer-Soll letter. For more discussion of the Berg letter see Krimsky, 83-84. See Appendix D for the Singer-Soll and Berg letters as they appeared in *Science*.

[2]For Dr. Boyer's views on the biohazard issue in 1975, see the oral history recorded just three months after Asilomar II. Oral history with Herbert Boyer, May 1975, p. 26. Recombinant DNA Controversy Oral History Collection, MIT.

the potential hazards of such research. From that came the Singer-Soll letter, which was published in *Science* and which called for a committee to be set up to study the problem and to recommend research guidelines.[1] Do you remember all that?

Boyer: Yes, vaguely.

Hughes: Do you remember that reaction?

Boyer: Yes. I don't remember that chronology. There was another letter written by Berg, I think, and Maxine Singer, and then a number of us signed it, calling for that Asilomar conference. But I had forgotten about the Singer-Soll letter. They were the organizers of the Gordon conference.

Hughes: Right, and the Singer-Soll letter asked for the formation of a committee of the National Academy of Sciences to consider the problem of recombinant DNA research, and from that came the so-called Berg letter. How did that work? The scientists who signed the letter didn't actually meet? Berg drafted the letter, and then circulated it for suggestions and approval?

Boyer: Yes, that's my recollection. I wasn't particularly privy to that inside work; I was just asked to sign the letter. I think primarily Paul Berg and Maxine had taken that task upon themselves. I was never politically savvy enough, even in the scientific community, to think about those things. We were pretty busy at that time doing a lot of different things.

### Thoughts on Potential Biohazards

Boyer: If I can recall my own feelings, I felt that this question of potential biohazards should be addressed. I never thought it was a significant problem. I thought it was overblown by the scientists, and it was picked up on by the media, and the whole thing got out of control and was very unfortunate. I don't think it served any real purpose.

---

[1]See Appendix D. For a journalistic account of these events see John Lear, *Recombinant DNA: The Untold Story* (New York: Crown Publishers, 1978, 69-94.

Hughes: And yet, you must have been uneasy enough to halt those experiments, because your technician Mary Betlach told me there were certain types of recombinant experiments that you, as she put it, "put on the shelf."[1]

Boyer: We were uneasy about them because we had the wrath of a large majority of the scientific community come down on our heads.

Hughes: Why weren't you particularly concerned about doing that kind of experiment?

Boyer: I think it was a rather informal accumulation of pieces of scientific information. I couldn't put them down in any particular order, nor could I claim that I had any major insight at the time. It was an impression I had, but I just couldn't imagine some of the scenarios happening. But it was hard to know what it was all about. It was just an impression I had more than anything. I couldn't argue it forcefully, although some people did. You could make any number of cases for the fact that these things [recombinant organisms] would not survive in nature. But there was always the "what-if" scenario which you couldn't counter. The problem that most scientists have hanging over their head is they can never say nothing can happen. You always leave yourself an out. We're trained that way. You can't say anything with certainty. [chuckles]

## The Asilomar Conference on Recombinant DNA Molecules, February 1975

Boyer: I thought the Asilomar conference was a nightmare. I thought it was so emotionally charged that it was counterproductive. There were a lot of accusations and shouting from the floor. I found it to be an absolutely disgusting week.

Hughes: What had you expected would happen?

Boyer: I couldn't say. I don't know if I had any expectations.

---

[1]See previously cited ROHO oral history of Mary Betlach.

Hughes: There were several working groups.[1] Were you asked to join one?

Boyer: Yes, I can't even remember which one.

Hughes: There was a plasmid working group. Was that it?

Boyer: I don't remember. I don't remember much about it. It was an exhausting week. I was so upset that I couldn't sleep. I didn't enjoy it at all. [laughs] I think that the whole thing was counterproductive.

Hughes: Well, the people who look back on that conference seem to feel that the intent was to end the research moratorium. There had been a voluntary moratorium that followed the Berg letter, which lasted roughly a year. Did the moratorium affect your research? Did it hold you up?

Boyer: I'm not sure. It might have. I could be very cynical and imagine that the moratorium gave everybody a chance to get on the same playing field. There were a lot of people learning how to do this [recombinant DNA technology] during that time.

Hughes: And you were teaching some of them, were you not?

Boyer: Yes, to a certain extent. These impressions I have would be very cynical. Scientists are strange people. [laughter] They don't have any more strength or less weaknesses than other people.

Hughes: So in a sense, the moratorium could have worked against you, by letting people more or less catch up?

Boyer: Well, that's possible, but there's only so much one laboratory can do. I'm not sure we would have done anything differently than we did.

## Diffusion and Development of Recombinant DNA Technology

Boyer: I think that the great thing about this technology was that it was very straightforward, very simple, and it didn't take much to transfer this technology into every laboratory. It just became so widespread in a

---

[1]The three groups were the Plasmid Working Group, the Eukaryote Working Group, and the Virus Working Group. Sheldon Krimsky, *Genetic Alchemy: The Social History of the Recombinant DNA Controversy* (Cambridge: MIT Press, 1982), 107-8.

very short period of time, and an amount of good things came out of it. What more could you ask for?

It's had a big impact, and it's nice to know that I was involved in the early stages of it and contributed to it. But every scientist brought his own little specialty, and his own insights. They improved it; the improvements just came at a remarkable pace. We spent a lot of this time developing a better plasmid, and developed a plasmid that became very widespread.

Hughes: Which one?

Boyer: It was called pBR322, and that was actually a fun thing to do. It made life a lot easier.

Hughes: Would you tell me about the development of plasmids, and specifically that one?

Boyer: Well, I just talked about how each scientist brought his own specialty and interest into play. The pSC101 plasmid that we used in the original experiments was a good plasmid, but it wasn't perfect. Each cell would carry maybe a couple of those plasmid molecules for bacterial chromosomes, so the ratio of plasmid to bacterial DNA was fairly small. Purification was that much more difficult because of that.

Hughes: Why did the cell only carry a little?

Boyer: It just has to do with the intrinsic replication properties of the plasmid.

Now, in contrast to that plasmid, Don Helinski and his colleagues at UC, San Diego and some other people had been working with another bacterial plasmid which didn't carry what one would consider a useful antibiotic resistant marker. It carried a gene that made a protein called a colicin, which would kill other bacteria, and which in turn carried the gene that made the cell that carried this plasmid resistant to colicin.

Now, the interesting thing is that this particular bacterial plasmid, if you inhibited protein synthesis in the bacterium that carried this plasmid, the bacterial chromosomal DNA stops replicating, but the plasmid replication just continues. So you can amplify this plasmid. Now, as it turned out, that plasmid was smaller than pSC101, so it was even better to work with, because the ratio of a plasmid to any cloned DNA would be much more valuable.

I had known Don because he'd been at the Hawaii conference, and we all sort of knew about these things. Don says, "Oh, we ought to try taking apart colicinE1 and analyze it with restriction enzymes. I can't remember exactly what the project was, but I think we published a paper on this.[1] One of the things that came out of this original experiment was that we found that by treating with the R1 enzyme, we could make what we called a mini-ColE1, which didn't make colicin but was still colicin-resistant. This was a very small piece of DNA. We actually used that at one point as a cloning vehicle, because you could use colicin resistance to select for transformance, and then you could amplify the DNA; you could get massive quantities of it.

Mary Betlach worked on mini-ColE1 extensively. We introduced tetracycline gene into the mini-ColE1. And then two postdocs, Herb Heyneker and Paco Bolivar, came along and said, "Well, there's another fragment of plasmid DNA that has a restriction site in the antibiotic resistance gene, so we can select for one gene and then just screen for the other one to ask if it's been blocked out, and then we'll know we have recombinants; we won't even have to analyze the DNA." So they went ahead and developed that in the laboratory.

Hughes: Now, that's pBR322?

Boyer: That's pBR322.

Hughes: What about pMB9?

---

[1]V. Hershfield, H. W. Boyer, C. Yanofsky, M. A. Lovett, and D. R. Helinski, "Plasmid ColE1 as a Molecular Vehicle for Cloning and Amplification of DNA," *Proceedings of the National Academy of Sciences of the United States of America* 71, no. 9 (1974): 3455-4359.

Boyer: That was the one with tetracycline resistance. It was the mini-ColE1 tetracycline, and we used that to make 322, and so on and so forth.

Hughes: How much during this period were you concentrating on developing the technology and methodology, as opposed to doing science with it?

Boyer: We were working a lot on the methodology. We really didn't do too much else at that time, because we were so busy working on methodology. And of course, you couldn't do much at that time, because of the moratorium. My focus had been on restriction and modification enzymes before that, so I was not particularly interested in trying to find a particular field that I could exploit with this technology. I had a few people come through the lab that would try to do some things, but it just never really got to the point where it became an interesting part at my own laboratory.

Research on *Halobacterium halobium*

Boyer: Subsequent to that, we got into working with *Halobacterium*, its purple membrane. Once I got involved with Genentech [1976], I stayed away from doing any research that looked commercially connected.

Hughes: What were you doing with *Halobacterium*?

Boyer: We had a friend in the Department of Biochemistry, Bob Stroud, and there was another colleague there, Walther Stoeckenius, who worked in this area. They were interested in cloning the gene for purple membrane in order to be able to manipulate it and do structural-functional relationships. We were interested in doing the same thing with the *Eco*R1 restriction endonuclease.

With the *Eco*R1 endonuclease we subsequently went on to make a lot of mutations in that enzyme, and to work on its structure with a group at the University of Pittsburgh and ask how the different substitutions in the protein would affect its enzymatic activity and its structure and function. It came along, but by that time, I was sort of thinking about retiring. We eventually lost support for the program, which was one of the things that instigated my getting the hell out of there.[1] [laughter]

Hughes: And it was this structural-functional research that you were doing

---

[1]Herbert Boyer retired from UCSF in July 1991.

at that point?

Boyer: Yes. Pat Greene was doing most of that work in my lab, and a couple of postdocs. It just didn't do well; it wasn't productive. It was a tough problem. Now, I'm not a structural biologist by any means, and we were working with the group back in Pittsburgh, so the interaction was extremely impeded by lack of communication, although we tried to get together a couple times a year and we talked on the phone a lot. Doing x-ray crystallography is long-term business.

## Distributing Plasmids

Hughes: Well, go back to the plasmid story, if you don't mind. I'm interested in the distribution, because you were doing a lot of that, from what I understand. How did that system work? Were there restrictions?

Boyer: There weren't any restrictions. All we asked for was a letter that they would comply with the NIH guidelines for recombinant DNA.[1] That's all.

Hughes: Anybody in the world could ask for plasmids?

Boyer: Yes.

Hughes: During the moratorium, did you stop distributing plasmids?

Boyer: No, I think we gave them out, with the understanding that they had to comply with the guidelines of the moratorium.

## Revisiting the Biohazard Issue

### NIH Research Guidelines for Recombinant DNA Research

Hughes: Talk about the guidelines, because as you well know, they were fairly stringent when they were first set up [1976], but by the late 1970s, 1980, they were pretty relaxed.

Boyer: They weren't real relaxed. I mean, you still had [university] biohazard committees, so everything [research proposals] had to go through there. An incredible waste of time and money. But that's bureaucracy for you.

---

[1]See Appendix D for a copy of the NIH guidelines as published in *Nature* in July 1976.

Hughes: The biohazard committees were a waste of time?

Boyer: Oh, yes. In retrospect. I think there was the gradual realization by most people, not everybody--there are still a few zealots out there, neo-Luddites, who like to think this could be the end of the world if they turn these crazy scientists loose. But I think there was a gradual realization there was no real threat [from recombinant DNA research] to life on our planet.

Hughes: The emphasis of Asilomar was on the potential biohazards.

Boyer: Yes.

Hughes: Gradually, as the practical applications of this technology became evident, focus shifted to the commercial possibilities.[1]

Boyer: I don't know if that had any real impact. It was a rationalization that could be used. But at some point you could say that there were x number of benefits of recombinant technology and there were no known incidents of anything harmful. It didn't matter to the logic of the conclusion, I think, that was used in the politics of the rhetoric.

## Opponents of Recombinant Research

Hughes: Well, one formidable opponent, or I presume he was formidable by his standing in science, was Robert Sinsheimer. He was particularly worried about genetic engineering "breaching the species barrier." Do you remember that argument?

Boyer: Yes.

Hughes: Did you think there was any validity to that argument?

Boyer: No, I didn't. I think it was a specious argument. I think the species barrier is an assumption. I don't know how you would define it or how you would support it. There was an old genetic observation that you couldn't get a viable offspring in conjugation of two different species, with notable exceptions, one being the jackass. But I don't understand the applicability of that general notion to recombinant DNA technology.

---

[1]See Susan Wright, "Recombinant DNA Technology and Its Social Transformation, 1972-1982." *Osiris* 1986, 2: 303-60.

Hughes: I think it was more an emotional one, rather than a scientific, in that nature has set up what man has defined as different species, and to cross the line separating them was crossing into some unnatural area.

Boyer: Yes. I've never seen Bob Sinsheimer emotional. [laughter] I can't understand why he took this stand. I think he had a certain philosophical bent to him which may have accounted for this position, I'm not sure. But he was an outspoken critic, and everybody's entitled to their own opinion.

Hughes: Then there was George Wald.

Boyer: George Wald, yes, well. He's a little different than Bob Sinsheimer.

Hughes: In terms of emotion, are you thinking?

Boyer: [laughs] I have no idea. I could never understand the guy. Or her [Wald's wife, Ruth Hubbard].

## The Role of the American Society of Microbiology

Hughes: Why wasn't the American Society of Microbiology [ASM] pulled into this debate? Or was it? The regulatory apparatus seems to have been located in NIH, which is probably appropriate as the major funder of research, but why wasn't the American Society of Microbiology more directly involved?

##

Boyer: Let me put it this way: I think the National Academy of Sciences had a cross-section of scientists in many different areas that could be called upon. Microbiologists were involved in the Asilomar conference, and the subsequent NIH guidelines, and so on and so forth--people like Stanley Falkow and a number of other people. Stanley had a reputation in the medical microbiology field and was listened to.

But I can't see any major problem with the ASM not being there in the debate. They probably didn't want to be involved. [laughing] I don't think the organization was set up for that. It's not an advisory body to the government like the Academy of Sciences. So I don't see any big glaring omission in their absence from the deliberations. Now, I

think they had a number of conferences and things like that, and discussions which dealt with it. But as a deliberative body, no.

### Concerns for Safe Technique

Hughes: There are indications of tension that arose at Asilomar between those with a molecular biological orientation and those with a microbiological, particularly in terms of appropriate microbiological technique and safety issues. There were implications that molecular biologists did not have training in microbiology and were not using proper technique. Was that a subtheme of the recombinant debate?

Boyer: I think it was part of the rhetoric, part of the concern. There were some microbiologists who probably were overly concerned about putting *E. coli* into the sewer, which would be like peeing in the ocean, as some say. When I was a graduate student, postdoc, I used to grow ten liters of bacteria and put the effluent down the drain. And you would sonicate bacteria in the laboratory without even taking great precautions.

Now, if you're working with a serious pathogen, you're working with *Bacillus anthracis*, which causes anthrax, then you're not going to do that, because you'd only do it once and you would be gone. So there would be a strong selection against people who were that dumb. [laughter] Just prior to that [the recombinant debate], there was the whole concern about growing large amounts of animal viruses, and in particular animal viruses that caused cancer in animals. And you could see that there would be some concern about that. I had concerns about a lot of laboratory techniques when I was a graduate student and postdoc.

Hughes: Were you instructed in safe techniques?

Boyer: You were only instructed in sterile techniques, because you needed to conduct your experiments under sterile conditions in order to be able to get definitive or interpretable results. But I can remember as a graduate student and as a postdoc one of the preferred ways for rupturing bacterial cells was to use sonication. I have tinnitus and hearing problems today because of sitting in the cold room sonicating bacteria for long periods of time, and nobody ever thought to buy ear

plugs, which I did when I got my grant. That was one of the first things I did.

But, you know, just exposure to some solvents carries some danger. When I was a graduate student or postdoc, some fellow was electrocuted. He was doing some paper electrophoresis, and the tank broke and he was flooded and electrocuted. Subsequently, I remember Howard Goodman had safety procedures and techniques which he had designed in his laboratory at UCSF. So those things impacted us. A lot of people were aware, but I don't think there were ever any serious problems caused by growing bacteria in a laboratory. We didn't talk about large quantities; we were talking about ten liters, twenty liters. Which is nothing, when you think of the industrial fermentations.

But I think it was just the usual ego and academic backbiting that was going on. And that's what I found distasteful about the whole thing. There were a lot of personality interplays, and people were trying to dominate and make a place for themselves. That is my interpretation, anyway.

Hughes: You're talking now specifically about Asilomar?

Boyer: Yes.

Hughes: Not the whole episode?

Boyer: Oh, yes. Universal. Transcends all meetings and episodes; it's nothing new.

I am a great fan of Marie Curie's story, or even Albert Einstein's biographies, or Robert Oppenheimer's, and the backbiting there-- It happens all the time. Major confrontation. People won't talk to each other.

Hughes: It's probably a function of reaching a certain position of power, regardless of what field you are in.

Boyer: Or trying to reach it.

Hughes: Or trying to reach it.

Boyer: Thank God I don't have to worry about that any more. I found it more distracting than anything.

Hughes: The distraction from science, I'm assuming, is what you're talking about. Did that begin with Asilomar?

Boyer: No, I found Asilomar to be one of those emotional encounters that you have every so often in your lifetime. But no, I found there was more tension and dissension after I started Genentech. That was a much more difficult problem.

Hughes: Well, let's save that for next time.

Boyer: Yes, tune in again next week.

## Potential Cloning Experiments

[Interview 3: April 7, 1994 ##

Hughes: Dr Boyer, we're looking at a letter that you wrote to Dr. Fink.[1] Who was she?

Boyer: I'm not sure. [laughing] She was probably a project officer. She may have been involved with the recombinant guideline office [Recombinant DNA Advisory Committee].

Hughes: That's what I suspected. She was at the NCI [National Cancer Institute]. This letter was written in March, 1976, and it contains a list of experiments that you were planning to do but didn't necessarily do, all involved with cloning. I wondered if these experiments were representative of the sort of research you were doing in the mid-1970s.

Boyer: I think some of the experiments on there were things that we thought we could do, but we just didn't have the wherewithal to do everything. In some cases, other laboratories focused on the projects. We just

---

[1]Herbert Boyer to Dr. Fink, Division of Cancer Research National Cancer Institute, 22 March 22 1976, (AR 86-7, UCSF Library).

didn't feel that we could do everything, and couldn't compete with a lot of laboratories that focused on one thing or another. So we were, I guess, looking at a lot of different genes that could be studied and cloned, but I don't think we had the size of laboratory or number of people that would be necessary to do that. I think after a few years, we tried to re-focus our activities because we were just doing too many different things.

Hughes: I went through the annual reports of the Department of Biochemistry and Biophysics, and it seemed to me that your research focuses over time were protein-DNA interactions and then *Halobacterium*? Were those really the two themes?

Boyer: Yes.

Hughes: It also seemed to me that it was very basic research. Was this deliberate, so that there would be no question of commercial application?

Boyer: No, I don't think so. I just think that was our interest in the lab, and we certainly did not have the capacity to explore anything commercial. It was being done in biotech companies, and the amount of energy and resources you need to do something like that were way beyond what we had there in the lab at the time.

Hughes: I noticed on that list in the letter to Dr. Fink that there were two shotgun experiments, which generally were a particular worry to those concerned about the possible consequences of recombinant research.

Boyer: Oh, I think that was a concern raised originally, but by the time we were doing it, the guidelines were fairly clear about what you needed to do to accommodate the guidelines, so I don't know, some people could have been worried about them, but we were following the guidelines.

Hughes: Did the guidelines specifically mention shotgun experiments?

Boyer: I can't remember now, but I think they did.

## Blunt-end Ligation

Hughes: In the annual report of 1976, I'd like to quote from something you wrote.

Boyer: Sure.

Hughes: "Most notably, we introduced the use of chemically synthesized restriction endonuclease substrates which can be covalently joined to DNA through 'blunt-end' joining with T4 ligase."[1] Why was this particularly notable?

Boyer: I'll have to try to put it in some context. There was a report early on in the literature that blunt-ended DNA could be ligated. It really wasn't followed by other laboratories until a year or two after the publication when Wally Gilbert confirmed it. Because the sticky ends were available, people weren't considering blunt-end ligation too seriously.

But in our collaboration with [Arthur] Riggs and [Keiichi] Itakura at City of Hope [National Medical Center], we were able to blunt-end ligate some chemically synthesized DNA that contained an R1 site that we had available to some chemically synthesized DNA that they had, which was the lac operator. In essence, what we were able to do was to make sticky ends, or put restriction sites on any piece of DNA that we wanted to. Rather than rely on the random distribution of sites in the natural DNA, we were able to introduce them at unique sites. So that was, I think, a pretty significant step forward at the time in terms of being able to manipulate genes and rearrange them.

Hughes: Is there any particular advantage of blunt-end ligation over sticky-end?

Boyer: It just gives you a lot of versatility which you didn't have before.

Hughes: Because you can ligate virtually anything?

Boyer: Yes.

## Collaboration with John Rosenberg: Protein-DNA Interactions

Hughes: Is there anything you want to say about your work with John Rosenberg on *Eco*R1?

---

[1]Department of Biochemistry and Biophysics, UCSF, Annual Report, 1976, p. 27.

Boyer: Well, I had met John Rosenberg at the City of Hope, when we were collaborating with Riggs and Itakura. Rosenberg was actually interested in protein-DNA interactions, and in particular the structure of protein-DNA interactions. The group down there had synthesized the lac operator and was trying to get a co-complex of the lac operator with the lac repressor protein in order to determine its structure.

That really didn't progress, and John and I got to talking one time about the possibility of using the *Eco*R1 endonuclease and a chemically synthesized or some derivative of chemically synthesized R1 site as a model system for protein-DNA interactions. Through collaborative efforts, we were able to get large-scale quantities of the protein and the DNA, and John was able to crystallize the complex of the DNA and the protein, and work on its structure.

Then we entered into a fairly long-term collaboration to try to use that structure to examine the contacts made between the protein and the DNA, and to dissect out some of the specifics of unique protein-DNA interactions. It was very slow work. I'm not quite sure where it stands now. We have collaborated for a number of years now. I haven't talked to him for some time, so I'm not quite sure where that project stands, or if he's still even working on it. But we made a lot of mutants of the R1 endonuclease in our lab, site-directed mutagenesis, and analyzed those changes with respect to the function of the enzyme--its ability to interact with DNA. Unfortunately, we were unable to keep the funding going in our lab to follow that up. So we dropped that research, and then I retired [July 1991].

Hughes: [laughs] The two might be connected.

Boyer: The two are probably connected, yes. Research funding was limited in the late 1980s and early 1990s, and we didn't have enough money to really run an aggressive project; we just had a few people. It was a little disappointing that we couldn't follow up with that. But life goes on, and there are other model systems around, and nobody seems to care too much about how these proteins interact with the DNA at the molecular level. They are good tools, but as a model system, they just weren't that exploitable. People are more interested in other types of proteins that have more relevance to protein-DNA interactions and control mechanisms, whereas this was just a straight model. But it was a fruitful collaboration; we got a number of publications out of it.

Hughes: Do you think your funding problems are indicative of the trend towards research having foreseeable application?

Boyer: Yes, I think it is.

Hughes: How do you feel about that?

Boyer: Well, I think there's enough basic research now to keep things going. I don't know how I feel. There's a limited amount of money available. Science is good enough today that you can do good molecular work with a very complex organism, even humans and other multicellular organisms, which have more direct relevance to science. So I don't know if it's good or bad.

Hughes: That's interesting that you say that, because I think of your work--I mean recombinant technology--evolving from very basic research--bacterial genetics, endonucleases.

Boyer: Yes. Well, I don't quite know how to respond to that. The stuff we did, whole-gene genetic engineering technology, I think opened up everything else. But that doesn't mean that there aren't some very interesting phenomenologies, and in microbes or other model organisms. But you can certainly work with the human immune system, and the amount of information you can get out of it with technology and knowledge that we have today is very good. So I think by using more relevant model systems, you're not compromising anything in terms of the basic research.

Hughes: You're saying that recombinant technology is one of the ways making it possible to investigate systems that are more directly relevant to humankind?

Boyer: Yes. Well, it's the standard tool.

## Nucleic Acid Sequencing

Hughes: In these annual reports, I noticed that at one point you said that you used sequence analysis using both the Sanger and the Maxam/Gilbert techniques. Why would one use both techniques?

Boyer: I can't remember many of the specifics now, but they both had their advantages and disadvantages. Some cases, it made sense to use one; some cases it made sense to use the other. I think it depended on the type of templates you had around in order to carry out the experiments. I don't even know what the standard procedure is today. I think Maxam/Gilbert may be the standard form now, just because of improvements in the technology.

Hughes: Was John Shine doing all this work?

Boyer: Oh, there were a number of people doing it. John did sequencing, but it got to the point where most of the people in the laboratory were able to do it. It was not really difficult once you got some experience in it. The toughest part was figuring out all the parameters for the gel electrophoresis and the resolution of nucleotides of different lengths. The chemical reactions were pretty straightforward--after they were worked out, of course. That was a very nice piece of work on the chemistry that led to [Allan] Maxam and [Walter] Gilbert's method, and [Frederick] Sanger's work was just another unique thing that Sanger did.

Sanger was an interesting guy. He got two Nobel Prizes, both for sequencing, one for sequencing proteins, and one for sequencing nucleic acids.[1] He was the first to sequence a protein, insulin. Then he worked out sequencing for DNA. Very nice guy, unassuming, not arrogant, very helpful.

## The *Smithsonian* Magazine Article and the NIH Guidelines

Hughes: The public recombinant DNA controversy arose in the mid-1970s, and feeding into that was the reporter from the *Smithsonian*, Janet Hopson, who spent three months in your laboratory in 1976. How did she come to be in the laboratory?

Boyer: I can't remember the details. I think she said she came with the idea of writing a story about recombinant DNA technology.

---

[1]Frederick Sanger won the 1958 Nobel Prize in chemistry for his work on protein structure. In 1980 he won again for his contributions to the determination of base sequences in nucleic acids. He shared this second Nobel with Walter Gilbert of Harvard and Paul Berg of Stanford.

Hughes: She was actually doing a little research.

Boyer: Well, I think she tagged along. I don't think she did a lot.

Hughes: The problem, of course, was that at one point in her article, which was not all negative, she said that some of the people whom she encountered at UCSF were rather casual about their adherence to the NIH guidelines, which, with the inflamed atmosphere on the public level concerning recombinant research, stirred things up a bit further, I suspect.[1]

Boyer: I think it was a little more complex than the way she described it.[2] What I recall at the time, a lot of serious scientists did not think there was anything dangerous about cloning and genetic engineering. They really couldn't see, except for maybe some rare instances, that there might be something really dangerous. When people have that attitude and when people have that perception, you have a hard time enforcing regulations that you don't think are necessary.

So I think there was a lot of discussion on the part of many people, and they were very denigrating of the guidelines, and they talked about it freely with her. But as far as I know, they went through the guideline procedures when they were doing experiments. I don't know of any instance where people blatantly violated them. What she means by "casual," I don't know. But I think people, particularly the postdocs, were fairly cynical about it all. But we tried to make them follow the guidelines, and as far as I know, they did.

---

[1]Janet L. Hopson, "Recombinant Lab for DNA and My 95 Days in It," *Smithsonian* 8, no. 3 (1977): 54-62.

[2]Boyer responded to Hopson's article with a letter to the *Smithsonian* that corrected the "factual misrepresentations" in the article. *Smithsonian* 8, no. 5 (1977): 10.

I had the same reservations. I think we discussed them before. I don't think there was anything really dangerous about recombinant DNA research, but you had to go through these procedures in order to satisfy the guidelines.

Hughes: Did the discipline in which a person was trained affect degree of adherence to the guidelines?

Boyer: I don't think it made any difference. Microbiologists have a long history of working with virulent organisms. But I think the procedures for handling virulent organisms in some cases were more rigorous than the ones imposed by these guidelines.

Hughes: But there was not that history in biochemistry.

Boyer: I understand your point. I don't know if that had any effect or not. Of all the scientists I've ever encountered or worked with or had come through my lab, I don't think any of them ever worried about any danger to themselves, which is the first level of concern everyone would have. I think, as I said, people followed the guidelines, but I don't think anybody was ever worried about anything.

## Use of an Approved but Uncertified Plasmid

Hughes: Well, related to what we're discussing is the pBR322 episode in which this plasmid was used in research at UCSF before it had gone through the entire NIH approval process.[1] It had been essentially approved, but not certified, and the certification had to come from the director of NIH, Donald Fredrickson. In the confusing period in the mid-1970s when the Recombinant DNA Advisory Committee and the guidelines were being set up and communication was largely oral, not by letter, the plasmid was used and insulin sequences actually obtained. It was your lab, of course, that supplied the plasmid. Mary

---

[1]For a popular account of the pBR322 incident and other aspects of the "race" to clone the insulin gene, see Stephen S. Hall, *Invisible Frontiers: The Race to Synthesize a Human Gene* (Redmond, Washington: Tempus Books, 1987). For an account of the Stevenson hearings, including transcripts of testimony, see Lear, *Recombinant DNA*, 181-272. The transcripts of the Boyer-Rutter testimony are in UCSF Library, AR 86-7 Carton 2, Folder 82.

Betlach told me that she was very clear that it was not certified and that she did tell everybody who asked for a plasmid the difference between approval and certification.[1]

Boyer: I have no direct knowledge that the plasmid was used surreptitiously before it was certified. This work was done in Howard Goodman's lab, and at that time, Howard and I had separated our joint grant into two halves. We were not collaborating together, because of personal differences. So I had no information about what was going on. They were very secretive about it because of the big race to clone the insulin gene. So I had no direct knowledge of what happened. All the information I have is hearsay, which is essentially what you stated before. So other than that, I really don't know anything.

## The Senate Hearings, November 1977

Hughes: You were on the spot during the Senate hearings on recombinant DNA research, which came along in November, 1977.

Boyer: Yes.

Hughes: You and Dr. Rutter were called in to testify. Why you? Goodman would have seemed to have been the logical candidate.

Boyer: Well, I don't know. I guess maybe I had more visibility.

Hughes: He may have been on sabbatical still too.

Boyer: That's very true. It could well have been.

We got a request from that subcommittee [on Science, Technology and Space] which Adlai Stevenson III chaired. They asked us to come back, and hell, we even had to pay our own way to testify for that hearing. Best I can remember, they wanted to understand what was going on. They were thinking about legislation to regulate recombinant DNA research, and they wanted our thoughts about it, et cetera, et cetera. So I went back there all prepared to tell them what I thought about it, and I read a statement. In essence, I expressed the concern that I just told you about, that if they were going to impose

---

[1]See previously cited ROHO oral histories of Mary Betlach and William J. Rutter.

guidelines, make sure that the guidelines fit the risk, because if you didn't do that, people were not going to follow the guidelines.[1]

Well, they didn't care anything about what I had to say. They were looking for headlines. That's just another one of those lessons that you get in life.

Hughes: Dr. Rutter said that you didn't make elaborate preparation for the hearing, and the questioning on the Senate floor was aimed at finding fault with--

Boyer: It was an inquisition; there was no question about it.

Hughes: Which you hadn't expected.

Boyer: I certainly wasn't prepared for it, and I certainly didn't have enough presence of mind to respond the way I would have liked to. I should have told them what I thought. But I was a pretty naive guy going up there. It was the first time I'd ever been before a Senate hearing, so I didn't know how to respond. So we just sat there and took our licks and got out of there as soon as we could. You never feel the same about politicians after you experience something like that.

##

Hughes: I read that after seeing drafts of the Senate hearing testimony, you and Dr. Rutter wrote letters to Senator Stevenson.[2] I didn't find your letter, but Dr. Rutter wrote that he came to the hearing to give information and was resentful of its "inquisitional manner."

---

[1]The testimony is summarized in Lear, *Recombinant DNA*, 181-214. Another description of this incident appeared in *Science* in September of 1977. Nicholas Wade, "Recombinant DNA: NIH Rules Broken in Insulin Gene Project," *Science* 192 (30 September 1977): 1342-5.

[2]William J. Rutter to Adlai E. Stevenson, Chairman Subcommittee on Science, Technology and Space, 22 November 1977, (AR 86-7, UCSF Library).

Boyer: I was, too. If we had known that was going to happen, I'd have had a lawyer there. We thought it was going to be the same sort of give-and-take that scientists are used to. Scientists aren't beyond being devious and Machiavellian by any means, but we don't go into things like that expecting to have an august body such as the Senate trying to carve you up for their political platter. We thought we were doing great things. We were doing molecular biology at the cutting edge of technology, and doing beneficial things, and here were these guys trying to nail us to the cross.

Hughes: You might have said it discreetly, but somehow or other the word was gotten to the Senate floor that the somatostatin gene had been cloned.

Boyer: We hadn't published it yet, as far as I can remember, but I had told Paul Berg about it, and he wanted to know if he could mention it. I'm very vague on the details, but I remember I talked to Paul Berg, and he may have told Philip Handler [president of the National Academy of Sciences]. I think they used that as an example.

Hughes: Of the practical benefits that might come out of recombinant technology?

Boyer: Yes.

Hughes: Did that make any impression?

Boyer: I don't know; I wasn't there when he did it. It probably didn't. It made the newspapers, some headlines. I remember Handler describing it as an achievement of the first order, and I remember that because our patent attorney at Genentech said, "Ah." He underlined that and said, "This will be used in the patent application." [laughter]

Hughes: Nicholas Wade wrote an article which appeared in *Science* right before the Senate hearing.[1] It described disturbing elements of the pBR322 episode, which we've already discussed. He also referred to a

---

[1]Nicholas Wade, "Recombinant DNA: NIH Rules Broken in Insulin Gene Project," *Science* 192 (30 September 1977): 1342-5.

nonprofit corporation called the California Institute for Genetic Research, which he said the insulin team had set up.

Boyer: I think Bill Rutter set this up. I can't remember the purpose.

Hughes: Was it to commercialize recombinant insulin?

Boyer: I just don't know. I remember hearing about it, but I don't remember what it was about.

The UCSF Biosafety Committee

Hughes: As I understand it, there was no formal biosafety committee at UCSF before the recombinant question came up.

Boyer: No, not that I know of. There was the radiation safety arm at the university which monitored disposal of isotopes and contamination in the laboratories, things of that sort. There was a committee to review clinical studies, to make sure patients had informed consent and so on and so forth. That was the backdrop. I think it was those examples that brought forth the idea of having a biosafety committee.

Hughes: You're right about the precedent. In June of 1976, Vice Chancellor Leslie Bennett appointed a campus biohazards committee which he suggested might use the Committee on Human Use as a prototype.[1]

---

[1]See Appendix E for papers relating to creation of a UCSF biosafety committee. For further information on the background for and foundation of the committee, see (AR 86-7, UCSF Library).

Was there anything unique about the structuring of the human use committee?

Boyer: I don't know anything about that committee. I don't know how it was structured or what sort of review they did. I think they devised a consent form and things of that sort, and they had some medical ethicists on the committee.

Hughes: Well, that might have been it, because that became true of biosafety as well. Do you remember that Al Jonsen was on it?

Boyer: Yes. The committee served its purpose, and essentially what it did was channel all of the recombinant DNA experiments through one committee, so one was aware of what was going on throughout the department. It became standard operating procedure that it would go through that committee before a grant request was made, if the grant request was involving that sort of thing [recombinant research] and hadn't been an existing grant request. In those cases, you had to tell biosafety what you were doing.

Hughes: This, of course, was a university committee. Had there been some federal mandate that an institution doing recombinant research establish a biosafety committee?

Boyer: I think so. I'm not sure, we may have set this up before the guidelines came out; I can't remember the chronology on it. It seems to me we were in the forefront of that.

Hughes: The NIH guidelines came out in July of '76.

Boyer: Essentially, the committee was just a clearinghouse. You had checkpoints on a piece of paper; people told you what they were doing; yes, that conforms to the guidelines. It really didn't do anything other than that. I think at one point, Dave Martin, who chaired that committee for a while, looked into some of the activities of the insulin group, but other than that, I don't think there was much to it other than a perfunctory organization.[1]

Resulting Controversies

Hughes: Apparently, some people felt that it was a waste of time. According to the minutes of a meeting in 1978, Christine Guthrie, a member of the biochemistry department, resigned, stating: "In view of the recent decision by NIH to remove essentially all power from the hands of the local committee, I cannot justify deflecting further time or energy from my scientific research." Do you know what she was talking about? It sounds as though something had happened at the level of NIH, weakening the power of the local biosafety committees.

Boyer: I don't remember anything about that.

Hughes: Did the biosafety committee have to deal with any of the neighborhood groups, one of which was in the vicinity of UCSF?

Boyer: I don't recall.

Hughes: There wasn't an organized neighborhood protest group?

Boyer: I can't recall anything like that. Later, during the Laurel Heights controversy,[2] [Chair of Medicine] Holly Smith was asked to explain

---

[1]In a letter of protest to Donald Fredrickson, director of the NIH, on 14 April 1978, Dr. James E. Cleaver, Chair of the UCSF Biosafety Committee, argued that too much authority was vested in Bethesda. Cleaver to Fredrickson, 14 April 1978, (AR 86-7, Carton 2, UCSF Library).

[2]In the mid-1980s UCSF purchased the 100,000 sq. ft. Fireman's Fund complex in Laurel Heights, and Chancellor Julius Krevans announced the university's intention to relocate a variety of academic programs including some research activities from the School of Pharmacy to this new location.

the type of research going on at UCSF, and someone accused UCSF and him of introducing AIDS into the population. It's not easy to deal with that.

Risk/Benefit Analysis

Hughes: One of the stumbling blocks in the early days of recombinant research was how to assess risk/benefit before there was much data.

Boyer: There was a lot of discussion about that. I don't think anybody ever could put a quantitative handle on it. But people talked about risk factor ratios ad nauseum, but never said anything.

Hughes: How could you, before you had done sufficient recombinant research?

Boyer: Well, everything we knew about plasmids and microorganisms pertained. We knew these constructions that we made in the laboratory weren't that easy to maintain. You had to be very careful about them, because you would lose the plasmids if you didn't check them and put the selective force back on them. So all the microbiological work on virulence that had been done led to a very low expectation of disaster. But it made good copy.

P-3 Facilities at UCSF

Hughes: Do you want to comment on the P-3 facility, which was created in the biochemistry department in the mid-1970s? I think there were only five labs that were, at least in the beginning, permitted to use it, presumably those that were doing recombinant work.

Boyer: I think it was available to anybody that wanted to use it. We had one built on the ninth or tenth floor of Health Sciences East in a little space up there very early on, even before the--well, I guess after--the guidelines came into effect. Then we put one up on the fifteenth floor.

Hughes: These were both P-3?

Boyer: Yes. But when we got the one on the fifteenth floor, I think they may have dismantled the other one. I can't remember. It eventually got to the point where the guidelines became refined with respect to containment, and experience was gained in doing this type of work. So a lot of these experiments were declassified, and the P-3 facility wasn't used that much, wasn't required, wasn't needed. I don't know if such a facility is around any more. I don't even think anybody at UCSF works with any virulent viruses any more.

The Q Fever Scare

Boyer: But I'll tell you, one of the worst things that happened to us at UCSF was on the fourteenth floor, right below my laboratory. We'd get off the elevator and walk past the fourteenth floor laboratories and then up the stairwell to the fifteenth floor. You could take the Medical Science [Building] elevator to the fourteenth floor, but that was all, and then you could walk over to Health Sciences East. These people were working with sheep embryos and grinding them up in Waring blenders. A whole bunch of us came down with Q fever, which is caused by a rickettsial virus. One of the guys who worked on the elevator in the animal tower got it. I think he died from heart failure, but it was related to the stress. This was about 1980, or 1981, something like that.

I sort of figured it out. My dishwasher came down with this syndrome. It was a high fever, achiness--it was miserable, because I got it also--and she was actually hospitalized. I got a call from the doctor. When they asked her what she worked with, she told them she worked with bacteria and recombinant DNA. They called me up, and asked, "You work with recombinant DNA?" And I said, "Yes, but I'm sure it's nothing related to what we're doing in our laboratory."

Then I found out that she had been diagnosed as having Q fever, and they couldn't figure it out, because usually people who live on farms get this, not in the city. And I knew what they were doing on the fourteenth floor, so I wrote a letter to the chancellor telling him. It turned out that when he got my letter, he'd gotten a notification from the public health department in San Francisco that they had traced a whole bunch of cases of Q fever to UCSF, located on the fourteenth floor. I had it; it was terrible. That was the worst thing that ever

happened to me in my career as a scientist, getting infected with a rickettsia.

Hughes: It's ironic, isn't it, after all the scare about what you were doing with recombinant DNA?

Boyer: Yes.

Hughes: I'm impressed that Q fever was diagnosed.

Boyer: Well, they were totally stumped, and they ran a whole bunch of tests, and finally did a fluorescent antibody test on her blood.

Hughes: Was there publicity?

Boyer: Yes. Not much, but it got some flak.

## III GENENTECH, INC. AND THE COMMERCIALIZATION OF RECOMBINANT DNA TECHNOLOGY

### Formation in 1976

Hughes: Well, the next step as I see it is the formation of Genentech. Had Bob Swanson approached anybody before he came to your laboratory?

Boyer: He said he took a list of names associated with the publicity on Asilomar and went through it alphabetically, which means Paul Berg must have turned him down. I suppose I was next on the list. It was a telephone introduction. He wanted to talk, so I had him come to my lab on a Friday afternoon at quarter to five. He introduced himself, talked about what he wanted to do. Did I think the technology was ready to be commercialized? He said he had access to some money, and I thought it would be a good way to fund some postdocs and some work in my laboratory, because we always needed some money to do that. We spent a good deal of time that evening talking about it.[1]

Hughes: Had you on your own before you met him thought in any concrete way of doing something like this?

Boyer: Yes. I had thought about the technology being ready to be commercialized, and had discussed it with at least one drug company that I can recall, but they weren't really very interested in it. I got

---

[1]See Appendix F for a sculptor's representation of the initial meeting between Herbert Boyer and Robert Swanson.

Miles Laboratory to start making some restriction enzymes. I went there and showed them how to do it, make R1 endonuclease. But I had been thinking about it.

I got an idea for this when my oldest son was tested for growth hormone. He was on the lower end of the growth curve, and the pediatrician wanted to test his growth hormone levels. So my son went in and did the overnight hospital stay, and did the somatostatin block-release, and that measured the release of growth hormone in a twenty-four hour cycle. It turned out he had normal levels of growth hormone, and the pediatrician said that he felt that he would grow to an acceptable size based on that, and even though he was in a lower percentile, it was nothing to get too worried about. I didn't even know that kids were treated with human growth hormone. Then he told me how difficult it was to get human growth hormone to treat dwarfism. I think at the time I may have even told my wife, "You know, we could make human growth hormone; all we have to do is isolate the gene." And this was before Bob had gotten in touch with me.

So I had had these little seeds of thought, fantasy more than anything. But I had no idea how you would start a company, and where you would go, what you would do. Of course, in my position on the faculty at that time, I wouldn't do anything like that; it would have been counterproductive, no question about it. But when Bob came along, he explained venture capital to me. He had this desire to start a company of his own, and he didn't want to start out in the usual fields in the Bay Area at the time, computers or running shoes or other things that were popular at that time. He wanted to do something different, and that was why he was looking. He had read a lot about the technology, and thought it might be useful.

I said, "Sure, why not." We formed a partnership, and during the partnership, we put together a business plan. He got some money. He was with Kleiner & Perkins and Associates, which did venture capital deals, so he knew about that end of it, and he had watched a number of companies develop by virtue of his participation on boards and things like that.

So he quit that job, and he got a little office in the corner of the Kleiner & Perkins outfit and paid rent on that. I think our original funding was $50,000. That paid his salary and rented the telephone, and so on and so forth. We designed the first experiments, which we contracted to my lab and the lab at the City of Hope and also at Cal Tech, because one of the scientists that was involved with that was a student at Cal Tech, although he was working at the City of Hope [Richard Scheller].[1] I insisted that Bob go to the Contracts and Grants office at Berkeley and set this up under the prescribed guidelines that they had in effect, which he did. He was very careful about all that, and did all that work. Then we started out.

Chemical Synthesis of DNA

Boyer: Our first plan was to synthesize human insulin. We were going to do it chemically because I had had experience with chemically synthesized DNA by that time. So we had the sequencing, chemical synthesis of DNA, and genetic engineering and the cloning thing. All of that was available either in my lab or I had access to it. I thought it was very important that we have chemically synthesized DNA, no matter what we did. I thought that was the key.

Hughes: Why?

Boyer: In order to identify genes, in order to adapt genes into different vectors, to modify them so that you could get maximum production--any number of reasons. At that time, it wasn't that easy to purify messenger RNA and make cDNA; you need the gene. And so with the chemical synthesis of DNA, all you needed to know was the sequence of the protein, and then you could make the gene.

So we were going to start out with human insulin, and when we started out I told Bob, "The key to this is to have chemically synthesized DNA." I told him about Riggs and Itakura. So I called Art Riggs, and he said yes, he was interested in doing this. So we gave Riggs and Itakura stock in the company.

Hughes: Are they the only ones that had synthetic DNA technology?

Boyer: No, there were a couple of other labs around at the time. I think Itakura was a postdoc or a student, I can't remember which, in [Saran

[1]Richard Scheller became Vice President of Research at Genentech in March 2001.

A.] Narang's lab, who had trained, I believe, with [Har Gobind] Khorana. Khorana had done the first major chemical synthesis of DNA at the University of Wisconsin, and chemically synthesized DNA was part of the approach to breaking the genetic code. Then there was [Marvin] Caruthers's laboratory at the University of Colorado, Boulder. Actually, Dave Goeddel was getting his Ph.D. in that laboratory, and went on to become one of our best scientists at Genentech.

But there were not very many labs around doing this. Narang's laboratory developed new techniques, and it was the phosphotriester method rather than a phosphodiester method-based synthesis that made it more efficient and faster.

##

Boyer: The problem with chemically synthesized DNA was that you could make a vial full of this stuff, but then you did experiments and you'd use it all up, and then you'd have to start all over again. People didn't particularly care to keep synthesizing DNA because it wasn't all this interesting to do. And not only that, once you had a synthesized piece of DNA in substantial quantity, it was not pure. There were a lot of improper pieces of DNA in there. It wasn't as pure as one would like for a chemical reagent.

The cloning of chemically synthesized DNA brought a new approach to that, because we could chemically synthesize something, clone it, and then you would have it. We could grow, make large amounts of it, and every molecule would be chemically identical for all intents and purposes.

So there weren't a lot of laboratories interested in chemically synthesized DNA, for some of those reasons. Plus it took a dedicated laboratory facility. You heard the story I told at the Rutter symposium. I went to Rutter to try to get him to do that [start a facility for the chemical synthesis of DNA] in the department, and he sort of said no by telling me to go ahead and do it in my lab, and get my own money.

So we got those guys [Riggs, Itakura, Goeddel] signed up, and I think that was one of the key events. I think that gave Genentech probably a five-year lead in the industry, because we were able to do things that nobody else could do. They tried to do them in a much more difficult way, and weren't that successful at it.

Somatostatin: Demonstrating the Technology

Boyer: To backtrack a little bit, the first plan was to synthesize two genes for insulin, actually one for the A chain and one for the B chain--which we eventually did. But when Bob and I talked to Art Riggs about this, he convinced us that there was a faster and easier way to demonstrate the technology, and the product might have some commercial benefit. Turned out it really didn't. But he had already proposed to NIH that the NIH fund a project in his lab in which they would synthesize the gene for somatostatin and express it in bacteria.

Hughes: Why somatostatin?

Boyer: Well, somatostatin is a small protein. It's only fourteen amino acids long. It would be easy to synthesize the gene for that. At that time, it was still a laborious and time-consuming thing. And also, we would make it as a part of a larger protein which we could chemically cleave away from the majority of the protein, and there was a very sensitive radioimmunoassay for the protein. So it was much more straightforward as a model than doing insulin. What we needed to do was to show that we could actually make a human protein in bacteria, and that was key to the next level of funding, to get an independent laboratory, and hire people and so on and so forth.

Hughes: Had the rat insulin gene been expressed at this point?

Boyer: No. I don't think so. This was before that.[1]

---

[1]Walter Gilbert's group at Harvard expressed the rat insulin gene in *E. coli* in May 1978; the Genentech/City of Hope team held a press conference to announce the synthesis of the somatostatin gene on 1 December 1977. The somatostatin work had been accepted for publication when the press conference occurred and was published in *Science* (9 December 1977).

Hughes: So nobody really knew, once you got a clone, whether it could actually produce the protein. Were you worried about expression?

Boyer: No. You could imagine some potential scenarios, but they were so extraordinary that I didn't feel that they were a problem. But we were aware of the guidelines; we were working under the guidelines at the time. The guidelines said nothing about chemically synthesized DNA, chemically synthesized genes. In addition, we had the protein attached to a large bacterial protein, and then cleaved it off chemically. It would never be functional being made the way we constructed it.

Hughes: Was it an oversight that chemically synthesized DNA wasn't included in the guidelines?

Boyer: No, I don't think so. I think the big concern at the time was shotgun cloning of eukaryotic DNA. We would never have gotten it in those days, trying to do it that way.

So we did the somatostatin thing, and as it turned out, if the somatostatin is made de novo or with just a short sequence, it's degraded by the bacterial cell immediately. You can't protect it. It's made, but it's just not protected. The solution to this problem was to precede the somatostain protein with a large protein. So that was a major step forward in terms of going to venture capitalists to get them to put more money into it. So we had a benchmark that we had established.

Hughes: Was the actual research itself fairly straightforward?

Boyer: It was, yes. Well, there were a number of little setbacks along the way. We designed the gene by using the amino acid sequence of somatostatin, and just using the genetic code, you could design that gene. But the way it was synthesized was that you'd make one strand, and then you'd have an overlapping strand, and then you'd make several of those and put those all together, and then you'd clone them.

Well, it turned out a lot of the things we cloned, because of the imperfections in the chemical synthesis methodology, led to defective genes. They would have a nucleotide missing here or there when we would analyze them, and so on and so forth. But eventually,

we got the right ones, and we put it into a vector in which we had a short sequence of the beta-galactosidase gene in front of somatostatin so that it was read in phase, and you'd have a bi-complex. There was only, I can't remember the exact number, I think there were eight amino acids in front of somatostatin.

Now, the key to this was something that Art Riggs identified, and that was that somatostatin, being so small, had no methionine residues in it. So what we did was have L-methionine codon in front of somatostatin. So when you took that hybrid protein, you could treat it with cyanogen bromide and cleave the somatostatin at the methionine residue, so you'd end up with the somatostatin protein plus what was in front of it, and those could be purified from one another.

But when we did our first experiment, we couldn't detect anything. So we went back and checked everything. Then we knew that small pieces of protein and bacteria were degraded by a system that people had studied for a number of years. So we surmised that we needed a larger piece of protein in front of the somatostatin so that it would form a more or less natural protein structure and would not be degraded. So we put a big piece of protein in front of it, and that worked fine, and we were able to detect somatostatin.

## Expanding to South San Francisco, Recruiting Scientists

Boyer: That was the benchmark we needed. And at that point we got additional funding; I can't remember what. We rented some space down in South San Francisco where the company's based now. Bob got a secretary, and we hired three scientists. There was Dennis Kleid and Dave Goeddel and Herb Heyneker.

Hughes: Now, who found people such as these?

Boyer: I found the first people, although I think Bob actually somehow connected up with Kleid and Goeddel. I'm not quite sure what that connection was. They were at Stanford Research Institute, which is an independent contracting body. They were thinking about synthesizing genes, because of Dave's background, and actually Dennis Kleid had at one time been in Khorana's laboratory. Then the first director of research was an ex postdoc in my laboratory, Herb Heyneker. He had left as a postdoc, and we went over to the Netherlands to talk him

into coming back, and he did so. So those were the first three scientists that we had.

## Human Insulin

### The Race for the Gene

Boyer: Dave spearheaded the cloning of the A and B insulin chain genes, with the chemical synthesis being done at the City of Hope. And then we brought the chemical synthesis of DNA into Genentech per se. We got one of the postdocs, Roberto Crea, who was in Itakura's lab at City of Hope, to come up, and he set up the chemical synthesis lab and hired a number of chemists, and we were on our way.

Hughes: The race for the human insulin gene has a lot of drama to it. There was the Rutter-Goodman competition at UCSF, and then there was Wally Gilbert and his group at Harvard. Both groups moved out of the country to escape the NIH guidelines. You didn't have to because synthetic DNA did not fall under the guidelines. How much of a race was it?

Boyer: Well, you know, it was a significant one. The Goodman lab and the Rutter lab and the Gilbert lab were able to clone cDNA, but it didn't mean anything unless you could make insulin. Their approach was to try to enzymatically manipulate the insulin gene, the human or the rat gene, into a plasmid which would allow its expression. Of course, they'd be making proinsulin or preproinsulin and they'd still have to have some way to convert it into insulin enzymatically, which is actually the way it is done now. But that was in the very early stages in the biotechnology game, and they just couldn't get it expressed, and the key was to express it.

Once we had the A and B chains independently made, they could be mixed in the test tube after they were purified under conditions which would allow the sulfhydral bridges to form and you could make active insulin. I always felt that we had the best approach, because it was direct. I don't know whether or not it would have made in the long run a big difference with respect to what Genentech did--insulin is not the only product around. But it certainly added a great deal of credibility to the company, from the scientific point of view.[1]

---

[1]For a description of this and related events, see Hall, *Invisible Frontiers*.

## Joint Ventures with Eli Lilly and KabiGen

Hughes: Well, credibility, and also the association with Eli Lilly, right?

Boyer: Yes, Lilly was funding it.

Hughes: And Lilly was not only funding the Genentech team, but it was also funding the Goodman-Rutter.

Boyer: Yes.

Hughes: Now, did anybody think that was a bit odd?

Boyer: No.

Hughes: No?

Boyer: You know, if you've got the money and you can afford it, cover all your bets.

Hughes: [laughing] You bet on both horses.

Boyer: Yes. When Bob and I started out, I had suggested that we try to establish some joint ventures and have established pharmaceutical companies fund what we were doing in order to defray the costs. Although we had access to venture capital money, they were still treading water with respect to their comfort factor. So we went to KabiGen in Sweden and got them involved, because they were the world's supplier of human growth hormone, more or less, outside of NIH.

And then we got involved with Lilly. We knew we could never compete with Lilly. They had more or less the lock on the market for insulin since the thirties, when William Banting and Charles Best did the original experiments. It wasn't a big hit on their budget to fund the projects we were doing--pretty insignificant amounts. So we took that approach early on. That's how we got a lot of our funding.

Hughes: Why would Lilly be interested? Wasn't there plenty of insulin around from traditional sources?

Boyer: There were some problems with it. Lilly was concerned about the supply of cattle pancreas, and also the fact that there was some immunological response in a significant population. I'm not quite sure what it was, but if I remember correctly, it was that a reasonable number of people had immune reactions to bovine insulin, and so it would become less effective. And this also led to problems associated with immune reactive complexes like that. It just didn't work that well in some people. And if you have human insulin--

So I think Lilly's approach was, well, we'll give these guys some money, and if they can do it, good. It's not a big hit for our budget. If it turns out to be successful, we've got ourselves covered. What Lilly would be concerned about was if we could have demonstrated that it was possible to make insulin this way, they would have a major competitor.

Hughes: What was the result when you did get expression? Did that make for a longer-term relationship with Lilly?

Boyer: Yes. I can't remember the details of the contract, but the way a lot of these things were set up is that you had benchmarks. When you cloned the gene, they would pay you so much money; when you had expression, you made so much money; when you had a certain amount of purified material, there was another benchmark. So each benchmark triggered a more extensive slippage into bed with them.

When you set up a contract like that, the company is obliged to develop it. What they could do is they could have access to the organisms, and buy them for a fixed amount, and then never use them, and then you're stuck. You don't get anything for what you've done. So there was a triggering. They went into a massive development that Genentech could never have done by itself. It was a good move. I think their first facility to manufacture recombinant human insulin that they made was a $60 million investment. I think 80 percent of the world's supply of insulin today is human insulin.

Hughes: Is that so?

Boyer: At the market use, anyway. But they have a new process now.

I think we were set up so that even if they developed beyond what we did, if they had another approach to it, we'd still get the royalties. So we're still getting a royalty stream. I don't know how long that lasts, but it has a fixed lifetime on it.

Hughes: Was it common procedure at that time for big pharmaceutical houses to contract with smaller companies?

Boyer: I don't believe so. We were the first in the biotech thing. There could have been similar arrangements in the electronics industry.[1]

## Genentech's Primacy in Biotechnology

Hughes: Is Genentech the first?[2] The only other competitor that I can think of for that honor would be Cetus.

Boyer: Yes. Cetus preexisted Genentech. Cetus grew out of some instrumentation that was developed at UC Berkeley by Don Glaser. Don Glaser was a physicist who got a Nobel Prize for thinking up the idea of the bubble chamber to trace subatomic particles. Then after he

---

[1]For further information on the role of industrial partners in the commercialization of UCSF innovations, see *Interviews with John Clements*, (San Francisco: UCSF Campus Oral History Program, UCSF Library, 1998) p. 72 and *Interviews with Lawrence Crooks* (San Francisco: UCSF Campus Oral History Program, UCSF Library, forthcoming).

[2]See Appendix K for public reaction to Genentech's IPO in 1980.

won the Nobel Prize, he got interested in molecular biology. That was the heyday of microbial genetics.

His idea was to build a machine--he used to refer to it as a smart dumbwaiter--which involved screening of microorganisms for production of certain things, in particular antibiotics. This machine would scan Petri dishes for extraordinary events. So you could put tens of thousands of Petri dishes into this machine, and it would analyze everything and tell you, "Well, there's a mutant in plate 29, row 30," whatever.

He had NIH funding to develop the machine. I guess it worked okay. I don't know if any academic laboratory ever used this except his. Then, I think the NIH decided not to fund that anymore; probably didn't think there was much use for it. That's when he used that machine to start Cetus. They mainly contracted with pharmaceutical companies that made antibiotics and looked for improved production of antibiotics, where they would mutate organisms to look for a higher yield of an antibiotic, or maybe screen for new ones. And that was how Cetus got started. But they were not involved in genetic engineering when we started Genentech, as far as I know.

Hughes: So biotechnology in a more restricted sense, meaning genetic engineering, in that sense Genentech would be the first?

Boyer: I think so, yes. It was certainly the first one to demonstrate that the technology was feasible.

Hughes: Does Syntex figure in this picture?

Boyer: No, only sort of as a role model to a certain extent. They got involved in it later. We may have talked to them, but I don't think we ever came up with a joint program. I do remember when Bob and I were in the early throes of starting the company, and I guess the word got around, Stan Cohen came to me and tried to talk me out of that and to become a consultant with Cetus. He was consulting with Cetus at the time, and I don't think they had gotten into the genetic engineering business yet. I said, "No, I'll stick with Bob." Stanley took me to lunch to talk me out of that. He said, "I've heard that Swanson's just a gofer anyway." [laughs]

Hughes: You got the Albert Lasker [Basic Medical Research] Award [1980] for the somatostatin work, right?

Boyer: No, it was for the recombinant DNA work, with Berg and Dale Kaiser and myself and Stan.

There was another award, V. D. Mattia Award, which was 1977.

Hughes: And that was for what?

Boyer: That was given to Stanley and me for recombinant DNA work, although I talked about the somatostatin there.[1] No, I don't think I ever got an award for the somatostatin research.

Somatostatin Studies

Hughes: The expression of somatostatin obviously was an achievement that had tremendous implications in terms of commercial biotechnology. What did it mean scientifically?

Boyer: Scientifically it demonstrated that you could chemically synthesize a gene and express it in bacteria and recover a human protein from the bacteria.

Hughes: So it was quite an achievement on both fronts?

Boyer: Yes.

Hughes: Did people in the scientific world pay attention to that research?

Boyer: That's an interesting question; I haven't thought about it. We just dropped it after that. We didn't follow up.

I thought it would be interesting to look at the somatostatin gene, because it's so widespread; it occurs in the most elementary multicellular organisms. It controls the release of proteins from cells. It's a feedback mechanism. I thought it would be interesting to compare the evolution and to look at associated genes around

---

[1]In later years, Dr. Boyer won both the National Medal of Science and the National Medal of Technology. See Appendix L.

somatostatin. We tried to isolate somatostatin cDNA from pigeon pancreas, of all places. [laughter] Somatostatin is not only expressed in the pancreas, it's also expressed in the lining of the gut and in the brain. We were interested in seeing if there were different genes involved in the production of somatostatin in different tissues. A lot of these things, you have an idea, and you get an eager young graduate student or postdoc who's willing to try this. They try, and if it doesn't happen, then you go on to something else.

## More on Early Recombinant Research at Stanford and UCSF

[Interview 4: April 20, 1994]##

Hughes: Dr. Boyer, last time you mentioned receiving the Lasker Award with Dale Kaiser, Paul Berg, and Stanley Cohen. How did Kaiser's and Berg's work relate to what you were doing in recombinant research?

Boyer: How much of a factor it was, is how I would rephrase your question.

Hughes: Yes, that's fine.

Boyer: A lot of Dale Kaiser's research on the bacterial virus lambda dealt with the naturally occurring sticky ends that these molecules encountered during their life cycle. They were able to show that one could form circular molecules from the linear molecules by virtue of reannealing procedures, and that, I think, was a seminal finding.

Then there was work going on by other groups in which enzymes were being used to put homopolydeoxyribonucleotides on the end of DNA molecules. One could make poly A [adenosine] and poly T [thymidine] ends under certain conditions on these molecules, and you could get them to reanneal. Berg's work took off from that, and they used that procedure to reanneal a linearized SV40 [simian virus] DNA. I think that those papers were seminal.

Now, we had been working on trying to do similar things with quasi-plasmids, lambda DV Gal for example, and had not had any success with that.

Hughes: What happened?

Boyer: Well, first of all, we later found out that the R1 site that cut the lambda DV Gal actually cut it in the replicon, if I remember correctly, and so it wouldn't replicate. I'm not sure about the chronology of that. But when we were trying to do some in vitro recombination experiments, we were trying to use a polymerase reaction to put tails on these molecules. We didn't know at that time the sequence cleaved by the R1 endonuclease. I'm pretty sure that chronology is correct.

So I think these types of experiments and this background did relate to our work. When Berg published his paper, we had determined the sequence of the DNA cleaved by the R1 endonuclease.[1] As a matter of fact, I think those papers appeared simultaneously in the same issue of the *Proceedings of the National Academy of Sciences*.

Hughes: Which was deliberate?

Boyer: No, I don't think it was.

Hughes: Happenstance.

Boyer: Yes. Of course, some of the work in Berg's lab, Janet Mertz and another faculty member there, Ron Davis, had used some of our enzyme and had found that DNA cleaved by the R1 endonuclease was reannealable. This was very critical to spurring us along to do the in vitro recombination experiments. Of course, at that time, that was helpful in our determination of the sequence cleaved by the R1 endonuclease, so I think that work was critical to what we did.

Hughes: Were you talking directly with Berg's lab, or was this only through publication?

Boyer: No, we had communications, primarily because we were very generous in giving them the R1 endonuclease. We gave them what amounted to about a bucketful at a time.

Hughes: [laughs] A lot of endonuclease.

Boyer: Yes.

---

[1]J. Hedgpeth, H. M. Goodman, and H. W. Boyer. "DNA Nucleotide Sequence Restricted by the R1 Endonuclease," *Proceedings of the National Academy of Sciences of the United States of America* 69, no. 11 (1972): 3448-52.

Hughes: Well, anything more to be said about this part of the history?

Boyer: Well, as any scientist will tell you, his own work is built upon the foundation laid by many, many people and many experiments and findings, and to a large extent, what any one individual does depends on what was done before.

Hughes: It is a continuum. I remember what you said last time about your recombinant work making research possible in areas that had been closed before.

Boyer: Yes.

Hughes: There was so much happening in recombinant research from the mid-1970s on. Did you ever feel that the technology was outstripping the theory?

Boyer: Well, people will argue that this is a cycle of science, and that science has plateaus and quantum leaps. The quantum leap comes through technology, and then there's a plateau in which a lot of information is gathered and stored, and nobody quite knows what to do with it. And then this plateau goes on until another technology comes along, although the plateau after the recombinant DNA research I don't think was very flat. I think it was reasonably steep. The discoveries and the amount of information that have come along have been incredible. It certainly amazed me. I find it difficult to keep up with what's going on in science today, and I also am continually amazed by the excellence in the biomedical scientific research community.

Hughes: You think more so in recent years?

Boyer: It's cumulative. Well, let's see. How long has it been? Thirty-some years of being somewhat close to research, you get a little jaded, I suppose. But if I look back at when I started in molecular biology, it's unbelievable how it's come along.

Hughes: You're living in a golden age.

Boyer: Oh, yes. It's been a wonderful experience, no question about it.

## Genentech's Early Goals and Philosophy

Hughes: Well, we talked last time about the origins of Genentech. You mentioned that in one of the very early meetings with Bob Swanson you worked out a business plan. I was wondering how it was comprised, how detailed it was, and how accurate it turned out to be.

Boyer: Well, I don't know if there's any record anywhere; I don't know whether Bob ever kept anything. A lot of this was sketched on note paper and outlined. Bob would type up some of these things.

But when I say a business plan, we set out with a philosophy for the company. We set out with a self-imposed mandate that employees would share in anything that came out of the company, in terms of holding stock in the company. I insisted that we have the scientists publish their research in journals. Any proprietary information would have to be covered by patents. I felt this was extremely important for attracting the outstanding young scientists in the community that were interested in doing research in an industrial setting.

I also wanted to bring in scientists that were outstanding and have them have an opportunity to establish their own reputation, get their own recognition. So we tried to set up an atmosphere which would take the best from industry and the best from the academic community, and put them together. And then we set up some goals, one of which was to demonstrate that the technology was feasible.

I think I've told you about the City of Hope collaboration on somatostatin.

Hughes: Yes.

Boyer: There was potential that with the first demonstration in which we made somatostatin in microorganisms that this small peptide hormone might have some commercial success. But it never really panned out, even though it had a rebirth at Genentech at one point. Someone thought that there might be some potential for it, and I can't even remember what application it was now. It was called Project Phoenix. [laughter] But that never really panned out.

Hughes: The main point of the somatostatin project was to demonstrate the feasibility of the technology, wasn't it?

Boyer: Yes.

Hughes: If you got a product out of it, that was fine, but not the main point?

Boyer: Yes. And then we went on to start a research project to synthesize human insulin, which you and I covered.

Hughes: This was still part of the business plan?

Boyer: Yes, that was part of the original business plan.

More on the Joint Ventures with Lilly and KabiGen

Boyer: Also part of that plan, in order to fund all of this research, I suggested to Bob--I think it was my suggestion--that we collaborate with established pharmaceutical companies that had interest in products developed through recombinant DNA research. So that's why we went to Lilly with the human insulin. They funded the research, and we had benchmarks for achievements, and there were cash payments and rewards for that. That helped the funding. So rather than getting exclusive funding and essentially giving away most of the stock of the company for funding, we did this through collaborations and joint ventures with companies.

Hughes: Was that a new thing?

Boyer: I don't think so. Actually, I think that joint ventures had been worked out between companies, but I don't know whether it was done at this level. I just don't know enough about joint ventures in other companies at that period to say.

Hughes: Joint ventures weren't prevalent in the biomedical sciences, were they?

Boyer: No. I think that there used to be contracts between pharmaceutical companies and individuals and laboratories and universities even, but I don't think that there was this small company-large company relationship. I don't think it was too prevalent; it could have been, I just don't know.

We went off to Sweden to talk to KabiGen. They had been marketing human growth hormone, which they purified from pituitary glands

obtained from cadavers. So we approached them. There was a fellow Bertil Åberg there at KabiGen who was very much interested. I guess he played an avuncular role in the early days of Genentech. Then we set up a collaboration with them, and they were going to fund us to make the human growth hormone. We went in with a scientific plan, and so on and so forth. And then we talked to some companies about vaccines and things like that. We established a number of collaborations.

Hughes: Were the two of you both doing this, actually getting on planes and meeting with these groups?

Boyer: Yes. We would set it up around--if I had a meeting in Europe or something like that, I would go. And that's essentially the role I played in the early days; I never did any research at the company. Other than the contract in my laboratory, I never participated in research there at Genentech. And so after those initial excursions, I sort of backed off. Once we got going, once we did the insulin thing, we hired people to do all that stuff. Fortunately, I didn't have to do it any more.

## Boyer's Decision Not to Participate in Genentech Research

Hughes: Was it a conscious decision from the very first, that you would not participate directly in the research of the company?

Boyer: Yes.

Hughes: Why did you make that decision?

Boyer: There were several reasons for it. One is I wanted to continue my own research, which I couldn't do at the company. It just didn't mesh, although I had a contract for a while from the company, a modest contract to support some postdoctoral fellows. Part of their effort went into developing some clones, but it was never any high-powered direct project that would lead to a product; it was sort of an accessory thing. So that was one reason.

Another reason was I didn't want to manage a large group of scientists. I had enough of a taste of doing that at a small level to know that I didn't like it.

And third, as I said before, I wanted to make sure that the young scientists at the company were getting the recognition. I didn't want to have my figurehead overshadowing anything they did. So it was a conscious decision, and I think a good one.

And I don't think I had the interest to work on the development of products. Although it's extremely exciting, I just don't think at the time that I could have played the role of managing that. And frankly, Bob and I, we're great friends and everything, but I don't think we would have worked well together in an intimate setting like that.

## Promoting and Recruiting for Genentech

Hughes: I read that you have a real facility for translating science to the public. Is that a talent that you began to develop after the foundation of Genentech? I imagine that you had to sell the science that you wanted to do to the investment community. Am I right?

Boyer: Well, it's kind of you to say that. [laughter] I'm not sure how good I am at that. But I know we did a lot of dog-and-pony shows.

Hughes: Well, tell me a little more. How would that happen?

Boyer: In various ways. In the early days, it was essentially talking to the venture capitalists. I'd just give a little lecture on a blackboard in a venture capitalist's office--draw the circles, and the sticks, and the enzymes, and all this stuff, and explain it to him. I guess in order for me to understand something, I have to reduce it to the most simple terms anyway. [laughter]

Hughes: Well, I don't know about that.

Boyer: It just seemed to happen. I suspect that maybe some people would have a more difficult time with it than I did. And then we got to the point where we'd visit other companies in which you could get a little more scientific, and people had backgrounds that didn't require a lot of introductory remarks. But it was interesting for a while doing that. We had a lot of fun.

Hughes: It's interesting to me that you could do this, because you said before that you didn't particularly like the teaching.

Boyer: Yes. Well, you know, adults and professionals aren't nearly as critical to your face as students. [laughter] They don't get in your face and jeer, yell at you.

Hughes: I'm also interested in this recruiting process. That took a bit of selling. After all, you were selling a new concept to most biologists from an academic setting. What would you tell a Heyneker or whomever you were trying to convince to take what must have appeared at that time as a risky step?

Boyer: I don't know. I think there was a certain amount of risk in it for those individuals, although they were young, and I don't think it had a big impact on their career--although it could possibly have had that. I must tell you, I did not do a lot of active recruiting. We actively recruited Heyneker; I was involved in that. He was a postdoc in my lab, knew about the company, knew about Bob, knew what we were doing, and he had gone back to the Netherlands. We went over there to talk to him about it. He was going to be the first VP of research.

He was enthusiastic about it before he went back. I think that he went home for family reasons. He was interested in staying. So we went over and talked to him, and he came back. He saw more opportunities at Genentech than in an academic setting. He was an extremely gifted scientist, with a wonderful sense of humor.

Then I was also involved in recruiting at the same time Dennis Kleid and his collaborator, Dave Goeddel. We did all of our recruiting with Dennis Kleid. I remember Bob and I took him out to dinner and talked to him about coming to Genentech. He was at the Stanford Research Institute, just started there. They were writing grant requests at that time. He had interests along the lines that were congruent with Genentech's interests.

We didn't even talk to Dave. I didn't meet Dave until after he joined the company. I think Dennis went back to Dave and said, "Gee, I don't know about this place, Genentech," and Dave said, "I think we ought to do it." I think Dave was the one who encouraged Dennis that they go up together to Genentech.

Dave has become a very good friend. We enjoy fishing together, and we even share a ranch in Montana where we go fishing. I think Dave,

along with Bob, were largely responsible for recruiting a lot of the other people that came in after that. Which is the way it should have been. I may have talked to a few people here and there. I didn't actively do that. I was pretty busy myself. But there were certain individuals along the way that I helped recruit.

Hughes: Was it the technology itself that excited these scientists?

Boyer: I think there was a change in attitude around this time. I think there were many factors involved. I don't know how real they were, and how much each of them impacted on the decision-making process. But I noticed around this time a change in certain young scientists, with respect to doing pragmatic applications of their research. They were interested in making contributions to medical sciences, biomedical sciences, and they thought joining Genentech was an interesting way to do things. There were diminishing funds available to support research in universities; there were diminishing numbers of positions, and a lot of competition.

Opportunities at Genentech involved not only a very good salary and opportunity to share in the success of the company through purchase of stocks, but it also offered them facilities and resources.

##

Comparing Industrial and Academic Science

Boyer: One of the keys to research is the collaboration between different groups. I think research was much more efficient at the company than at a university, much more efficient. One of the things I find particularly gratifying is the number of scientific contributions that have come out of the company since its inception. It's a major source of scientific contributions.

Hughes: How would you define the differences, if indeed there are any, between the science that is done in a place such as Genentech, an industrial setting, as compared to science in a university?

Boyer: I've never been able to clearly define in my own mind what differences there are. Having been associated with both institutions, I find them remarkably similar. In an academic setting you apply for research funding from a government agency or some other funding agency, and you make the case for the research, why it should be

funded and what your research goals are, and you present your credentials, and a decision is made.

The only difference in an industrial setting is that you have fewer areas of science to which you can make application, so you have to fit your research within the overall goals of Genentech, although there are a number of scientists that have made enough contributions that they are essentially allowed to work on their own in some area that they find interesting. The company management feels confident that they will work towards something that will eventually benefit the company. I think a number of the scientists there have a certain percentage of their time where they can pursue things that they find interesting. But I think in both situations, you have to mold your research into whatever is currently favored by the funding agencies.

Hughes: Is it your perception that a paper that is published by a scientist at Genentech is received by the scientific community with the same credibility as one that came from UCSF or wherever?

Boyer: If it's a good paper, certainly.

Hughes: There is no stigma to the science that comes from industry?

Boyer: I don't believe so. Many of the papers that come out of Genentech are collaborations with scientists in universities and other academic settings.

## More on Early Corporate Goals

Hughes: Well, you mentioned goals in connection with that original business plan. Were those broader than production of somatostatin and insulin and the various benchmarks that you set up? Did you have some overarching goals?

Boyer: Yes. There were some goals, relative to the amount of cash flow, etc. We always had a goal of trying to break even, which I think for most of the years the company has been in existence, we managed to do. And we had goals in terms of cash flow and employees and so on and so forth. I can't remember much about those.

Hughes: Was there any stipulation about the general sort of contribution that you wanted to make in terms of products?

Boyer: Well, I can't remember the exact wording, but Bob would always say, "I'm not interested in hula hoops and tennis shoes." So we had very idealistic and altruistic goals in terms of making products that would somehow benefit society. That was part of the original goal.

Hughes: Did Bob Swanson come to you with some foundation in science, or did he have to pick that up?

Boyer: Well, Bob had an undergraduate degree in chemistry, and then he got an M.B.A. at Sloan Business School. And then he went into venture capital. He always said he never had a green thumb; he never did well in the laboratory. But Bob's a very bright guy, and he could talk technology. He was very eager to learn, and would always ask questions, and very good questions.

He didn't have the grasp that someone had that's been in the field for a long time. I can remember very early on telling him we needed to hire people in cellular biology, and I had to work a long time on him to convince him that cellular biology was an important thing to have represented at the company, but now it's a big component.

Hughes: His thinking was that it should all be done on a molecular--

Boyer: He was very focused; what we needed were genetic engineers and chemists to synthesize DNA.

Hughes: And that was it.

Boyer: Yes.

## Development and Scaling Up

Boyer: Talking about the science at the company, there's a whole other level of science which is different from the university, but extremely important, and that's in the development area. This is something that gets overlooked. A lot of the success in the development end of biotechnology comes from the interaction between the people in manufacturing and development and basic sciences. They work very closely together, and the accomplishments in the manufacturing of biopharmaceuticals in the last twenty years is just unbelievable.

When I was a graduate student, if you could get a couple of milligrams of pure protein, you did a good job. Some guys could get

a Ph.D. thesis for that, and then analyzing the protein. But in the commercial setting, when you have to make hundreds of kilograms of a protein pure enough to pass the critical eye of the FDA, that's a major step forward. I think that has had a big impact on the basic sciences as well, because it's made available large quantities of pure protein for structural work and other things that can be done. So that is different, because that's very directed research in which your goal is to make large amounts, pure amounts, and so on.

Hughes: Did you anticipate the problems that would be encountered in scale-up?

Boyer: We were so naive we never thought it couldn't be done. We knew that the pharmaceutical industry had a history of scaling-up products like antibiotics and amino acids, things of that sort. But this involves a whole different technology. I think the group at Genentech probably has been a leader in the field for developing manufacturing processes for biopharmaceuticals. There are still companies today that don't quite have that capacity, and they're still on the learning curve. And we're on a learning curve there also, but I think far ahead.

Hughes: Did you in retrospect make certain naive assumptions? I believe that there was the assumption that *E. coli* could do anything, and that turned out not to be the case.

Boyer: I don't know. I think from our first experiments, we had some indication that *E. coli* was not going to be universal. And in those days, everybody had their favorite organism they pushed as the choice. As it turns out, you can do certain things in bacteria, and you can do certain things in yeast, and you can do certain things in tissue culture. So yes, it might have been naive, but what's amazed me is just how efficient and how productive tissue culture is. Years ago, if you grew ten liters of tissue culture, that was a major effort. It took up all your space and a lot of technical support. Today, they grow ten, twenty thousand liters at a time, and have maximum production of a protein. I always maintain that the best attribute we had was our naiveté.

Hughes: [laughs] Anything was possible.

Boyer: Yes, right. I think if we had known about all the problems we were going to encounter, we would have thought twice about starting.

I once gave a little talk to a group at a Stanford Business School luncheon, and I took off on the title of a book by Jacques Monod. He was discussing evolution. The title of his little monograph was--pardon my French--*Chance et Necessité*. The title of my talk was "Chance, Necessité, et Naiveté."

Hughes: [laughs] Very apt.

Boyer: Naiveté was the extra added ingredient in biotechnology.

## Repercussions on the UCSF Campus

Hughes: Well, let's talk about how these developments were perceived in the Department of Biochemistry and Biophysics, on the campus as a whole, and in the wider scientific community.

Boyer: I'm not sure how accurate my reflections are. But at this point, my perception is that there was mostly a negative reaction in the department towards what I was doing. There were criticisms that there was a big greed factor, that I was compromising my research, a big conflict of interest. I had critics within the department, I had some friends in the department who tried to talk me into leaving, just dissociating myself with Genentech altogether. One colleague commented that he wouldn't touch what I was doing with a ten-foot pole. There were articles in *Synapse* [UCSF student newspaper].[1]

Bill Rutter was fairly supportive. I had gone to talk to him when I was first thinking about founding Genentech, and I told him what I was going to do and asked him what he thought. You heard my comment at the symposium in honor of Bill Rutter.

Hughes: Say it again for the record.

Boyer: I said, "Bill, I'm going to do this [found Genentech]. What do you think?" He said, "I think it's fine, and you should do it. Good luck. I've always wanted to start a company myself."

---

[1]See for example *Synapse*, 14 April 1977 and "Ire over School-Industry Meeting," *Synapse*, 4 March 1982.

After becoming aware of the comments of colleagues in the department and elsewhere on campus, the administration and the Academic Senate took a look at this. It was Chancellor [Francis A.] Sooy at the time, and Juli [Julius] Krevans was dean. My take was that they looked at everything we had done, and we had done it by the book. As usual, the Academic Senate waffled back and forth, waffled on it as only it can do.

Hughes: Let's stop for just a second. [tape interruption] Dr. Boyer, you just looked at some documents related to the Academic Senate and biosafety committee reviews. How did the issue come before the Senate?[1]

Boyer: I really don't know. I suspect that Keith Yamamoto wrote a paper--he was probably the most critical faculty member--maybe also Bruce Alberts and Brian McCarthy. I can't say for sure; I can only surmise that from some of the letters. There were probably others that had the same problem. I really don't have access to that information.

Hughes: One of the letters is from Laurel Glass to Sheldon Wolff, who was chair of the Committee on Rules and Regulations of the Academic Senate. Was that just a formality? She didn't have any real function in this other than to convey the complaints?

Boyer: I don't think she was instrumental in initiating it.

Hughes: The issue arose around the somatostatin research?

Boyer: I think that's probably when it started. I think Bob [Swanson] was very noticeable. He would come around the laboratory. I was on the fourth floor of the Medical Sciences Building at that time, [the location of the microbiology department]. Although I was a member of the biochemistry department [located on the ninth floor], I was still on

---

[1]Laurel Glass, Ph.D., M.D. to Sheldon Wolff, Ph.D., 11 January 1979, and Report of the Committee on Rules and Jurisdiction, San Francisco Division of the Academic Senate, 6 August 1979, (AR 86-7, Carton 2, Folder 94, UCSF Library).

the fourth floor. So it wasn't as if we were walking through the middle of the biochemistry department, and I don't know where all the observations came from, because a lot of those people didn't come down to the fourth floor. There were some other microbiologists around. There were a lot of postdocs coming around the laboratory from other laboratories in biochemistry.

Bob was in a suit, and you know how scientists dress. So he stood out. He was all excited and enthusiastic about this, and talked to people in my lab. There may have been people that resented the fact that others in my lab were on this contract, and they weren't.

But it's hard to go back and recreate the situation. It was very difficult for me. I had a lot of anxieties and bouts of depression associated with this. Here I thought I was doing something [laughs] that was valuable to society, and doing something that would make a contribution, and then to have the accusations and criticisms, it was extremely difficult. I think I got a $500-a-month consulting fee at that time, which was a big help when it came to getting by on an associate professor salary, whatever it was. And I got support from Genentech for some research in my laboratory, support for a couple of the postdoctorate fellows.

Hughes: For Herb Heyneker?

Boyer: Herb Heyneker and Paco Bolivar. And I think we had a little bit of support for the general operating funds of the laboratory. But it was difficult to deal with the criticisms and the tension and the notoriety. It was very distracting to me.

Hughes: Did it interfere with your research?

Boyer: It may have. Over a period of time, I felt ostracized. I resented the treatment that I got in the department. There were people that were supportive, so it wasn't universal. John Watson and Dan Santi were very supportive. But it wasn't easy.

Hughes: I can imagine.

Boyer: It wasn't easy. And the way the attacks went, I felt like I was just a criminal. But I always felt that what I was doing was right. I didn't think I was doing anything unethical or immoral. I never dreamed that the financial rewards would amount to what they did. The

potential was there, but I never thought about it. Bob and I had started out with 50 percent of the stock apiece, and then it got diluted out. But I never in my wildest dreams ever thought it would amount to anything. That's another example of my naiveté.

But the money was not a driving factor. To me, it was the excitement and challenge to do something like this. It was an opportunity to take the technology and the science to some pragmatic level, which a lot of people never had the opportunity to do. So I didn't have the same perception that my critics did of what I was doing. Of course, [laughs] you never agree with your critics.

But nevertheless, for whatever reason, rightly or wrongly, it did create a lot of anxiety on my part. I don't think there was a lot of dissension in the department. I think all the dissension was directed at me, so I don't think that there were factions that were neutral, anti, and pro, that were going at each other. I think larger groups of people that thought I was doing the wrong thing would get together and bitch and moan about things. But that's my recollection of the situation.

## Issues Arising from Faculty Relationships with Industry

Hughes: Were there policy changes that came out of the Academic Senate investigation? Was there, for example, definition of the relationship that a faculty member should have with a commercial concern?

Boyer: I think you should ask all the other members of the department that have started companies. [laughter] And those that have commercial relationships. I would imagine that many of them are involved today.

Hughes: I was actually meaning in a more formal sense. Did the university set up guidelines about consultancies and corporate relationships?

Boyer: I'm not sure there have been any formal changes. I should know about that as a director of the UCSF Foundation. There has been some discussion, if a company is born out of a university laboratory and a university faculty member, that the university should be rewarded with a stock position in the company. I think that must have its own problems associated with it as well, but the evolution has been towards a more--I hate to use the word liberal--interpretation of the relationship between the scientists and the companies.

I would be the critic now to say that one has to be on guard about conflicts of interest in industrial relationships. I think the conflicts are there, especially on the clinical side. I think there are big problems on the clinical side, and that has been dealt with in the past. I think there are occasional examples of real conflicts of interest between industry or pharmaceutical companies and universities, but I don't think they are any more numerous or prevalent than the instances of plagiarism and scientific misconduct solely within the context of the university. It's just humankind's nature to do misdeeds and cut corners and things like that. You only have to guard against them.

Hughes: When you talk about potential problems in the clinical area, what are you thinking of?

Boyer: I think there have been some changes in regulations, and I'm not sure at what level, whether it's just at the university or whether it's done by NIH. But the potential and the actuality of conflict of interest have been in cases where a company will engage a clinical department or professor at a university hospital to conduct clinical trials. If the clinicians are given the opportunity to obtain stock options or whatever, that's a real potential conflict. I think there have been some guidelines, rules, regulations, legislation--I'm not sure exactly to what extent--to guard against that. There have been some charges that I've read about in which this has occurred. I don't know how real it is, but the potential is certainly there.

That sort of thing is not going to go on. My feelings in relation to scientific misconduct are, if a scientist or clinician or whatever is going to falsify or plagiarize, that type of activity will not go unnoticed. If his publication or whatever is going to have any impact at all in science, you immediately find out whether it's right or wrong. And if the guy is falsifying his data, or if he continues to falsify his data and passes it off in the scientific literature, he gets the reputation of either not knowing what he's doing or actually falsifying material. And then he's essentially eliminated from the scene. There's a certain waste of money, but I don't know how to guard against it.

##

Hughes: I think the major concern of the Academic Senate committee was the potential for impedance of the flow of information. Have you been aware that with the rise of the biotech industry there has been a change in information flow in academia?

Boyer: My general perception is that this is not an attribute of the institution but of individuals. I've known scientists in academic institutions that won't tell anybody what they're doing, and they swear their laboratory assistants and fellows and students not to say anything to anybody until the work is published, because they don't want to be scooped. I'm sure there are instances in pharmaceutical companies and other industries in which people don't want their competitors to know what they're doing until they've done it. I think it's a matter of choice, and I think any individual or any institution has the right to do that.

I think the idealistic attitude, which I agree with--I do it myself--is to openly discuss ideas and results with people. Sometimes you tell people what you're doing. I'm not talking about myself, but I know of instances where people will hear information and they'll run back to their laboratories, and they've got a major group of people that they can put on a problem, and they'll solve the problem before the source of the information has an opportunity to do it. That's happened on numerous occasions, I'm sure.

So the give and take in science is a choice. It's an extremely efficient way to conduct science. One of the most enjoyable things about science is talking to other scientists about what you're doing. Their criticisms, their reactions, are extremely valuable in terms of how you conduct your research: You didn't think of this; you didn't think of that. Those interactions are extremely valuable and aid the process of scientific investigation immensely.

But everyone has the right to be secretive about what they're doing. Anything I did at UCSF based on a contract with Genentech was not secretive, I can assure you that. Herb Heyneker talked to everybody. He'd talk to the guy on the street corner waiting for a bus about what he was doing.

Boyer Speaks Out at the Gordon Conference, June 1973

Hughes: [laughs] Well, you have that reputation, too, at least according to Mary Betlach.[1] She also discussed the Gordon Conference on Nucleic Acids in June of '73 when you first publicly talked about what has become known as the Cohen-Boyer experiment. I read that you and Dr. Cohen had an arrangement that neither of you would talk about any of this work until it was published in the *PNAS* [*Proceedings of the National Academy of Sciences*].[2] But you did. So I asked Mary about that, and she said something to the effect--and I'm paraphrasing--"Well, Herb always wanted to talk about what he was doing. He probably got enthusiastic and just talked about it." Do you remember that?

Boyer: I don't remember that arrangement with Stan. However, Stanley was reasonably secretive about what he was doing.

Hughes: That was his general demeanor?

Boyer: That was his nature, and he didn't want to talk about it until it was in print or published. I'm sure I told him that I was going to talk about this. This was an important meeting, and this was the sort of place where you wanted to talk about things like that; you wanted to get the feedback. I'm sure I probably told Stanley I was going to do it, that I wanted to talk about it.

Hughes: I wasn't really meaning to pinpoint you on that particular point--

Boyer: No, no, I understand.

Hughes: --but rather to ask if your general way of handling scientific data was to be open with it.

Boyer: I have a hard time not talking about something like that.

Hughes: Isn't the point of the Gordon conferences to share information in an informal setting? Was there a stipulation that you couldn't talk about what wasn't published?

---

[1]See previously cited ROHO interview with Mary Betlach.

[2]John Lear reports that Dr. Boyer "got up and spilled the beans" at a Gordon conference session titled "Bacterial Restriction Enzymes and the Analysis of DNA." John Lear, *Recombinant DNA*, 69-70.

Boyer: No.

Publicizing Scientific Results Before Publication

Hughes: Do you remember the article in the *New England Journal of Medicine* in which Stanford's press agent talked about gene cloning by press conference?[1]

Boyer: I don't remember that.

Hughes: Well, it was a reaction not just to Genentech's press conferences; there had been several others. Biogen had had a press conference in relation to the interferon work, and UCSF had had press conferences about gene cloning. The point he made was that the pattern in science up until that time was that research should be published in a peer-reviewed journal before it was released to the press.

Boyer: I think that was generally accepted. I couldn't swear to this, but I thought the paper on somatostatin had been accepted for publication. I remember one press conference at UCSF, and there was one at City of Hope. I'm pretty sure that the one at UCSF, the paper was in print or had been accepted.

Hughes: Well, I can give you the dates--

Boyer: You're not going to go out on a limb and hold a press conference unless you know the work has been accepted or will be published. I don't think we ever did that. I don't know about other press conferences. And I think I only did one.

Hughes: Genentech held a press conference to announce the first complete synthesis in bacteria of a human protein, somatostatin, on 1 December 1977.[2]

Boyer: I don't know when that paper was published, but I do believe it had been accepted, because I remember being in Washington at the *Science* office going over galley proofs, I think it was November [1977]. I

---

[1]Spyros Andreopoulos, "Gene Cloning by Press Conference," *New England Journal of Medicine* 302, no. 13 (1980): 743-45.

[2]The somatostatin press conference took place 1 December 1977. The *Science* paper was published eight days after the press conference and one month after the Stevenson committee hearings. K. Itakura, R. Crea, et al., "Expression in *Escherichia coli* of a Chemically Synthesized Gene for the Hormone Somatostatin," *Science* 198 (9 December 1977): 1056-63.

had already talked about the work at the Roche Institute [of Molecular Biology] when Stanley and I got the V. D. Mattia Award in 1977.

Hughes: On September 6, 1978, there was another press conference, which I believe was held at the City of Hope, on the expression of the gene for human insulin.[1]

Boyer: Yes.

Hughes: Were you there?

Boyer: I was there. I didn't say anything, but I was there.

Hughes: What was the atmosphere?

Boyer: A circus. [laughter] I can't remember much about it. We had Dennis Kleid and Dave Goeddel and Art Riggs and Itakura and some other people who were involved in that research. I was not involved in it. I was not a co-author on that paper. It was held at the City of Hope to give the City of Hope a little P.R. For some reason or other, Dennis Kleid was talking to the press and answering questions. I think he gave them a description of what was going on. We had to get him off the podium, because he's such a loose cannon. [laughter] Dennis sometimes just doesn't think before he answers questions; he gets it all screwed up. So we were trying to get him off the podium and get somebody up there to take over.

There were some officials from City of Hope, and there was a physician-scientist at City of Hope--I can't remember his name now--but he was one of the father figures in the field of insulin and insulin therapy. He got up and gave a little spiel.

This sort of thing was more for the company's recognition and for the institution's recognition. I always hated these things. I couldn't stand to do that. I sort of got talked into it.

---

[1]Gail Bronson, "Bacteria Induced to Produce Insulin Identical to Human" *The Wall Street Journal*, 7 September 1978, p. 17. The press conference is described in Hall, *Invisible Frontiers*, 266, 267.

Hughes: So the message was for the public and for investors?

Boyer: That's what I meant. It was for the public and the investors. Also for the institution.

Hughes: It was not the way you would address the scientific community.

Boyer: No. Now, hell, you see all the time UCSF and other institutions have press conferences and news clips and whatever. I don't have any problem with that. I think you're always confronted with the issue of trying to educate the public.

Hughes: Well, you ran into trouble because you were a pioneer in these areas. It took people awhile to come around to these ideas.

Boyer: Yes.

Hughes: So you got the flak.

Boyer: Yes, I got the flak. [laughter] Well, that's all right. Looking back on it, as difficult as it was, I wouldn't change anything. I never thought about being a pioneer at the time, if that's the correct description of what I did. I wouldn't change anything. And disregarding all the angst and depression associated with it, it was pretty exciting, too. It was a real manic-depressive time.

Hughes: Well, that's a good point to stop.

## Details of the Cohen-Boyer Collaboration

[Interview 5: July 22, 1994]##

### Authorship

Hughes: Were there ever problems coordinating what was going on in your lab and Dr. Cohen's?

Boyer: No, the coordination was quite good, actually, because one of Stanley's postdoctoral fellows, Annie Chang, lived in the city.[1] She would bring materials and take things back, and that sort of arrangement worked very well. No, it wasn't difficult at all. We each did certain parts of the experiments, and then we got together and wrote the paper. The only problem we ever had was when we were

---

[1]At the time, Annie Chang was a laboratory technician. She later earned a doctorate.

trying to decide the authorship of the paper. We had some serious discussions about how to do that. But it all worked out.

Hughes: Do you care to elaborate on the order of authors?

Boyer: Stanley wanted to have a very prominent place in the list of authorships. I felt there were several ways to deal with it. So we ended up with a compromise, but it was no big deal.

Hughes: Why is Annie Chang second author?

Boyer: I can't remember how we decided to do it. Usually the two positions, or at least in bygone days, the positions of recognition were either the first or the last. So I think what Stanley and I compromised by putting our names in the middle. I can't even remember what the order was now.

Hughes: The order on the first paper is Cohen, Chang, Boyer, and Helling. And for the second paper, it's Morrow, Cohen, Chang, Boyer, Goodman, Helling.

Boyer: Yes.

Hughes: Was there a logic to the first order?

Boyer: No. I don't remember anything about it. It didn't make any difference, because the laboratories were both equally represented. Subsequent attribution of the work was to Stan and myself, so it really didn't make any difference. It was sort of silly, but that's the way people are. [laughter]

I don't know whether anybody's interested in this, but Howard Goodman's name wasn't on the first paper, because Stan Cohen was very insistent that it not be on there. And actually, Howard really didn't do anything with respect to the actual laboratory work. Howard and I had a collaboration, and Howard had the expectation that his name would go on every paper regardless of whether he was actually involved with it or not. Stanley was very insistent, since Howard hadn't done anything on the first paper, that his name not be included.

On the second paper, I insisted that he put Howard's name on the paper, even though he didn't really do anything. That was a very

significant--we talked about it occasionally. I said, "We've got to put it on there, because that's the arrangement that I have with Howard." And subsequently, Howard and I went our separate ways. To a certain extent, that was part of how it came about.

Hughes: The friction created by these encounters caused you to stop collaborating?

Boyer: Yes.

Hughes: Was it usual in science to put your name on a paper to which you really hadn't contributed?

Boyer: No, it's not that usual, but it does happen, although most people would not do that. All the work that Howard and I did together, we published together. Prior to this particular set of experiments, he had been involved. I can't remember, but I think since I set up the collaboration with Stan that we just did it ourselves in my own lab, and Howard wasn't involved with it. I can't remember why. But yes, that led to some problems.

I think scientists do have a lot of problems with collaborations. For example, Howard had a collaboration with Mike Bishop, and a lot of times they put Howard's name on their papers, and they didn't put me on. So I tried to point out to Howard--but Howard's idea was that that was different. [laughter] So you know, the weaknesses and differences in personalities, whatever. It happens. A lot of egos and jealousies.

Hughes: It happens, and it also influences science at times.

Boyer: Oh, yes, it slows it. You see it all the time. People are always fighting about things--recognition, egos.

## Recombinant Experiments with Eukaryotic DNA

Hughes: Well, I was interested in the conclusion to that first paper, and I'll quote if you don't mind.

Boyer: Sure.

Hughes: [reading] "The general procedure described here is potentially useful for insertion of specific sequences from prokaryotic or eukaryotic chromosomes or extra chromosomal DNA into independently replicating bacterial plasmids."

What interests me about that statement is the mention of eukaryotic chromosomes. Obviously, you were thinking several steps ahead.

Boyer: Yes. Actually we had been thinking of it even before we did those experiments, trying to rationalize and develop technologies for recombining DNA in vitro. It was something that at least I had been thinking about. It was fairly obvious at that stage when we did that first set of experiments that it was possible. But there were a couple of serious questions that had to be dealt with, which we did deal with in the second paper.

Hughes: I can see that the actual recombinant procedure itself would not be a theoretical problem. Presumably, DNA would splice with any DNA.

Boyer: Yes.

Hughes: But was not actual replication in *E. coli* a question in your mind?

Boyer: Well, there were several issues that we had to deal with. One was whether or not eukaryotic DNA had some signal or sequence in it which would prevent it from replicating in *E. coli*. There were known to be certain variations in eukaryotic sequences not present in prokaryotes, for example. And that was, I think, the most theoretical component of it. I never had any doubt that it would replicate.

The big problem we had in those days was that when we did the first paper, where we recombined plasmid fragments, we selected for genes from the two different plasmids, so we could pull the needle out of the haystack very nicely. Now, we didn't know the frequency of the events for molecular recombination. So when we went to eukaryotic DNA, at least in the early days, we couldn't select for recombinant plasmids in bacteria that carried the eukaryotic DNA. So we had a concern about just how efficient the in vitro recombination would be, and how easily we could recover a recombinant plasmid, since we could only select for the plasmid DNA.

So if you have a million plasmid DNA molecules, you can select for those after you recombine them with themselves. But we didn't know when those plasmids transform the bacteria, how many would carry the eukaryotic DNA. So we just did a blind screening. We selected for the plasmid, and then we would take the resulting transformants and examine them for a piece of the eukaryotic DNA, which had been well characterized so we could identify it quite handily.

Hughes: How, precisely, were you making the identification? Because you didn't have sequencing techniques yet, did you?

Boyer: Yes, the sequencing data was available, although we didn't do it. The choice of eukaryotic DNA was critical in this case. We just didn't take a random DNA. The reason we took the frog DNA, the *Xenopus laevis* DNA, was because at certain stages in the development of the frog, there is an amplification of the ribosomal DNA genes. They're repeated hundreds of times over. Because of the differential in the base composition of that amplified DNA, it could be purified away from the background of chromosomal DNA.

This work had been done primarily in Don Brown's lab at Carnegie Institution in Baltimore. He had given some of that DNA to John Morrow, who was at Stanford. He was a graduate student of Paul Berg's.[1] When I presented the first work at the Gordon conference [June 1973], John was there. He was still finishing up his thesis. We were talking after the discussion of my paper, and I said, "The next thing I want to do is clone some eukaryotic DNA. But we have to find the right type of DNA." We didn't want to use DNA tumor virus, which would have served the purpose equally well, because of concern regarding the potential biohazard.

John said, "Well, I've been looking on *Xenopus laevis* amplified ribosomal DNA. I know it's cut with the R1 enzyme, and you get discrete fragments of known size." So I said, "Gee, that's great. That's a potential eukaryotic DNA fragment to be cloned." John said he'd give us some of the DNA. I said, "Well, since you did some of the original work, why don't you join us on the paper?" I asked Stanley about it, being sensitized that way. [laughter] And Stanley agreed to that. Of course, John was at Stanford also. So that's how we chose the

---

[1]For Berg's view of this episode, see the previously cited ROHO oral history.

*Xenopus laevis* DNA--because it had been characterized with respect to size.

And then the other thing we had was, since it was a gene for ribosomal RNA, we could hybridize ribosomal RNA to the plasmids and show that they indeed were carrying the genes for the ribosomal RNA. So that was the key thing.

And it turns out that in those experiments, we tried to set up the in vitro recombination so that it had a good chance of working, but we just didn't know for sure how good that was. But I think about 5 to 10 percent of the plasmid transformants actually carried the fragment.

## DNA Fragment Closure Rates

Boyer: See, the problem with in vitro recombination is--this is a little technical--it's all based on the concentration of ends of the DNA. So if you have a very small piece of DNA, it can close on itself very quickly, because of the fact that one end is always close to the other in the concentration--the shorter the molecule, the higher the concentration of the ends within a molecule.

So what you have to do is, if you know the sizes of the fragments of DNA or have some estimate of them, you try to match the concentration of the ends of the plasmids with the ends of other fragments, so that they'll have a very high probability of finding another fragment of DNA and ligating together, rather than closing up. If you have very small molecules, they just close up so quickly, you can't put anything into them. So that was the problem that most seriously concerned us.

Hughes: Had that problem arisen in the earlier experiments?

Boyer: No, because we could select for the molecule, so you could get one in a million certainly very easily. So that was it.

Actually, Howard and myself and a postdoctoral fellow, Achilles Dugaiczky, published a paper.[1] We did a whole series of experiments on closure rates and intramolecular collisions.

---

[1]A. Dugaiczky, H. W. Boyer, H. M. Goodman, "Ligation of *Eco*R1 Endonuclease-generated DNA Fragments into Linear and Circular Structures, *Journal of Molecular Biology* 96 (1975): 171-84.

## The Species Barrier

Hughes: Implicit in the *Xenopus* work is the breach of the conceptual barrier between the prokaryotes and the eukaryotes. Was that an issue at all? Was it an issue for you?

Boyer: It wasn't an issue of mine. I think that barrier is largely artificial and just based on precedent and prejudice. Prokaryotes and eukaryotes are supposed to be different, but how different? All living organisms share some common origin. Prokaryotes and eukaryotes diverged a long time ago. The question I had was whether or not there was something in the eukaryotic DNA sequence which couldn't be replicated by the bacteria.

Hughes: Yes. So nobody looked at this work as being iconoclastic, tearing down this old concept?

Boyer: No. I think that concept went back to the animal husbandry days in which a species was defined as, if two organisms that appeared to be related could not produce offspring, they would represent two different species. So this species barrier was sort of an artificial Linnean concept.

Hughes: The idea that the species barrier is supposed to be inviolate crops up a bit later, as we have discussed, in some of the arguments against recombinant technology.

Boyer: I think it's a specious argument--pardon the pun.

## Preparing Purified Plasmid DNA

Hughes: Did the technicians, Annie Chang and, in your lab, Mary Betlach, play any more significant role in this work than was customary?

Boyer: No, but their expertise and technical skills were critical. In those days, preparing purified plasmid DNA was a chore. Now you can make plasmid DNA from a few microliters of bacterial cells; in those days we did liters. It was a major undertaking, a lot of work.

Hughes: Why was it made in such large amounts?

Boyer: We just didn't know how to do it on a small scale. It came quickly, but in the early days, that was the way everybody did it. If you wanted to make plasmid DNA, you made a couple of liters of cells and did the purification. Everything improved very quickly after that. Once everybody had to do it, then everybody was trying to figure out a faster way to do things.

Hughes: Including your lab.

Boyer: Yes.

## Diffusion of Recombinant DNA Technology

Hughes: Do you remember which specific lab groups took up this technology in the very earliest days?

Boyer: Oh, I can't think of all of them, but there were some people I knew who got involved. Don Helinski's lab at UC San Diego immediately got in touch with me and he sent some people up from his lab, because he had been working with a small plasmid called colicine E1. We developed from that plasmid replication bases for the series of pBR plasmids that became the standard cloning vector for many, many years. We developed those in my lab. So Helinski's lab was one of them. [Mark] Ptashne's lab sent a postdoc out for a summer or a little bit more. A number of people came through my lab who I can't remember. Gordon Tomkins jumped on it.

But there was a certain hesitation, because of the Asilomar conference, the pending NIH guidelines--a lot of laboratories didn't jump in right away, but soon thereafter, within a year or so.

Hughes: Was coming to your lab to get hands-on instruction the way to go?

Boyer: It was probably the fastest way to go early on, probably for the first year. Obviously, not everybody could come through the lab. We spent a lot of time with people coming and trying to clone various things. We got involved in a lot of collaborations which were distracting. But within a short period of time, a year or so, the techniques were commonplace. And then once people started it, other people made significant advances. I can't remember exactly who it was, but somebody cloned cDNA. They made, I

think it was, a rabbit hemoglobin cDNA. That was done in somebody else's lab.

And then [Thomas] Maniatis did a human genome bank, and they developed phage vectors and packaging vectors. It just sort of exploded after about a year or two. Although it might be that the explosion wasn't quite as extensive as I imagined. But I have a recollection that it was fairly quick.

### Effect of the NIH Guidelines

Hughes: Did the static after Asilomar put a damper on research and diffusion of the methodology?

Boyer: Oh, yes, no question about it.

Hughes: Was that a disappointment to you?

Boyer: It wasn't a real disappointment. I felt that it did slow things down. I'm not sure that it mattered. In five years, it probably didn't make a hell of a big difference. But at the time, there was a lot of frustration. We had a lot to do anyway. We could operate within the guidelines. So it wasn't that we didn't have anything to do.

Hughes: You said that you spent a lot of time on developing the methodology. Was that somewhat because it was difficult to do some kinds of research and it was a safe way out to focus on methodology?

Boyer: The methodology that we focused on was to develop what was euphemistically referred to as a containable plasmid, to do cloning in viably compromised cells. So we worked to develop a plasmid that would have diminished capacity to replicate outside of certain bacterial cells. Then we used bacteria that just couldn't survive in the real world. You could grow them in the laboratory, but they could never compete if they got out of the laboratory.

Hughes: The weakened bacterial strain was developed elsewhere, wasn't it?

Boyer: Yes, the weakened bacterium was *E. coli* chi 1776. Roy Curtiss and his lab had done that. He proposed that, and then we did all the testing of the plasmids in those bacteria--it was terrible. It was such a mess to work with those things.

Hughes: Why?

Boyer: They were barely even viable in the laboratory. To try to work with them was just miserable--your efficiencies were reduced, and it was difficult.

Hughes: Was it a struggle to keep the cultures alive?

Boyer: All you needed to do was keep the plasmid. You could make plasmid preps and store them frozen.

But in the long run, I don't think the NIH guidelines made a big difference.

## Commercializing Reagents

Hughes: Could somebody learn the technology adequately from your papers?

Boyer: Yes. I don't think there was any question about that. Part of the problem in those days was that a lot of the reagents were not available commercially, like restriction enzymes, and that's what we had. We had a number of key restriction enzymes and ligases, and we had been purifying plasmids and developing plasmid vectors. So those are key things. And then once the technology got going, there was a need to provide these things commercially. Nobody purifies their restriction enzyme today; they buy them. They buy the cloning kits, and the vectors, and all of that. It's a big business now.

Hughes: Was there more than one company that came in initially with those products?

Boyer: Yes. I can't remember which one was first. I actually went back to Miles Laboratory, and I think they were the first ones to supply the R1 enzyme. I went back and showed them how to make the R1 enzyme, because I was tired of giving it to everybody. [laughter] I wanted to get somebody else to do it for me.

Hughes: And they did commercialize it?

Boyer: Yes.

Hughes: And probably very successfully, in a monetary way.

Boyer: I don't know.

Hughes: Do you remember when that was?

Boyer: That must have been '74, '75. I went back to Elkhart, Indiana, for three or four days.

And then one of the other key things that happened soon thereafter was that Rich Roberts at Cold Spring Harbor screened microorganisms for different restriction enzymes and came up with a large number of different types. So these then became available commercially as well, and that was a big breakthrough.

Hughes: Well, anything more on recombinant DNA?

Boyer: No, I think we've probably overworked it.

## The Boyer-Cohen Patents

### The Process Patent, December 1980

Hughes: Now, the patents. I assume that the activity surrounding the patent application was centered at Stanford, and that Niels Reimers was the one who pushed the idea?

Boyer: Well, the story is as follows: After we had published our paper, I think it was the eukaryotic paper, the *Daily Stanford* did a story. I think it was Niels Reimers in the patent office there.[1] He called Stanley up and said, "You know, you should try to get a patent on this." Stanley said, "We can't get a patent on this; the research is supported by NIH." So Niels pointed out to him that that's not a restriction, that every university and every institution has a patent agreement with NIH.

Then Stanley called me and said that the Stanford office wanted the patent on it. I said, "Stan, you can't patent that; we're funded by NIH." I had the same misconception that Stan had. So he explained to me, he said, "No, Niels tells me that it's certainly patentable." Of

---

[1]Boyer refers to Stanford's Office of Technology Licensing. For Niels Reimers's perspective on the Boyer-Cohen patent see: "Tiger By the Tail," *Chemtech* 17 (August 1987): 464-71 and Niels Reimers, "Stanford's Office of Technology Licensing and the Cohen/Boyer Cloning Patents," an oral history conducted in 1997 by Sally Smith Hughes, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 1998.

course, the UC patent office didn't consist of much in those days. I won't comment on what I think it consists of these days.

But in any case, Stanford got in touch with the UC patent office, and they agreed that the Stanford office would handle the patent. I can't remember the name of the lawyer who did it. They had a patent attorney in the South Bay, Bert Rowland.

And that's how it got started. It was certainly not Stanley's idea or my idea to do it. Very few molecular biologists knew anything about patents, their place in science and business, or even in the vitality of our country.

So we initiated this and Stan and I spent a number of hours explaining what we did to the patent attorney, and going through the technology and the terminology and how things were done, and helping him with the prior art and so on and so forth. It took a long time to write the patent. It was a ground-breaking patent in a way. (In 2001, Stan and I were inducted into the National Inventor's Hall of Fame.)[1]

Hughes: Right. Were you very aware when you were writing it that this was going to set precedents?

Boyer: Yes, Niels told us it would probably be the first patent that everything involving recombinant DNA would encompass. But since we had published a paper without filing a patent, it was not viable outside the United States, or maybe North America. But certainly the patent wouldn't be recognized in Europe; it was only viable for things done in the States. But it's been a very lucrative patent nonetheless.

I must admit, I didn't have a lot of patience with patent law and trying to figure it out. So I just told Niels everything I knew, and the guy went ahead and did it. Stanley helped him out quite a bit; they were always working on it together. I tossed in a few ideas.

Hughes: Has it stood the test of time?

Boyer: Oh, yes. I don't think it's been challenged. It only has three more years to run. The seventeen years is almost up.

---

[1]Boyer added this sentence during review of the transcripts.

Hughes: Was your only hesitation in filing a patent application the legality concerning NIH?

Boyer: Yes.

Hughes: So even though this wasn't something that was done in molecular biology, there was no feeling that it was somehow inappropriate?

Boyer: No, we were just ignorant. But the rest of the scientific community was just all over us, because they were ignorant also.

Hughes: For patenting?

Boyer: Yes. I can remember going to a meeting on the East Coast, perhaps 1976, and it was the subject of conversation. I think Stan was there, actually. Both of us were there. We gave talks, and people were jumping up and yelling, "Is it true you're patenting recombinant DNA? How can you do that?" Now everybody has been educated towards that.

Hughes: What was their main concern?

Boyer: They thought that once it was patented, that they couldn't use it in their laboratory. It was just gross ignorance. I was ignorant as well to it, but necessity called me to learn something about it.

Hughes: I read that the licensing fees are relatively low, and that that was done for a purpose.

Boyer: This was a strategy that the Stanford office came up with in order to encourage companies to recognize the patent, and also to start cash flow very early in the lifetime of the patent. It took years. Now there are fairly substantial worldwide sales based on this technology, but

that didn't start until about ten years ago. So the Stanford office wanted to get some cash flow coming, so for a fee, the companies could sign up, and then they were guaranteed that they'd have a very reasonable royalty on any products they sold. So it was negotiated ahead of time. They didn't know whether it was going to work or not for a lot of products, so the risk fee was up front--it was like taking an option. Still it's been, in terms of money, the best patent that UC and Stanford has had.

Hughes: Oh, by far and away, isn't it?

Boyer: Yes.

Hughes: Well, what we've been talking about is the process patent, right?

Boyer: Yes.

## The First Product Patent, August 1984

Hughes: And then there's the product patent, which I understand was expected to be awarded approximately two years later [1982]. And wasn't. There were several problems.

Boyer: I don't remember the details.

Hughes: One of them was that Helling thought his name should be on the patent.

Boyer: Yes.

Hughes: And then there was also a question of a paper which had been published in *New Scientist* on October 25, 1973, one year and one week before the patent application was filed.[1] The paper was not written by any of the authors of the patent, but by Edward Ziff. This surprised me, because I naively assumed that in patent law 'prior publication' meant by those intimately concerned with the research, not by a bystander.

---

[1]See Edward Ziff, "Benefits and Hazards of Manipulating DNA," *New Scientist* (25 October 1973): 274-5, and John Elkington, *The Gene Factory: Inside the Genetic and Biotechnology Business*, (New York: Carroll & Graf Publishers, 1985), 35-36.

Boyer: No, not necessarily. That's a strange thing about patent law.

Hughes: You weren't really involved in that problem?

Boyer: No.

Hughes: Of course, the denouement was that in 1984, the product patent was issued.

Boyer: Yes. Well, patents are important, although a patent position is not guaranteed. As one of my lawyer friends says, it's nothing more than a key to the courthouse door. It doesn't guarantee anything. You have to defend it, because it will certainly be attacked. But this one wasn't, I think because once people paid the fee up front, that was sort of a recognition of the validity of the patent. Patents are such a standard operating procedure now. People became sensitized to the value of patents, the value to the university and to themselves, and so now they are standard operating procedure.

Hughes: You alluded to the undeveloped state of the UC patent office. Did this business accelerate its development?

Boyer: Yes, it did. I won't say any more.

Hughes: [laughs] I gather that's a sensitive subject.

Boyer: Yes, it is.

## IV SUMMARY COMMENTS

### Boyer's UCSF Laboratory

Hughes: Well, let's move to what I hope is not a sensitive subject, and that's the general atmosphere in your laboratory at this period. Could you characterize it?

Boyer: Overall?

Hughes: Yes, in terms of the pace of the work, and the degree of communication that was occurring.

Boyer: I found it to be very stimulating. I think most of the people, not only in my laboratory but other laboratories at UC, were excited about the potential of the technology, and all the things going on, the

recognition. People worked hard. We were there for long days and on weekends, and we'd go in in the middle of the night to look at things. Well, we talked before about the condition of the laboratories. They were just antiquated, very difficult places to work. But nevertheless, it was very exciting. It's probably worse today, but the space constraints were difficult then. We used to put boards over the sink so people would have a place to run gels and do experiments.

Hughes: Amazing.

Boyer: At a [laboratory] bench about the size of this sofa where you're sitting, you had three people working there.

Hughes: People willingly gave up their private lives? This was just what one did?

Boyer: Yes.

Hughes: The whole lab?

Boyer: Yes. Some people were more intense than others. Some people worked a regular day, but most people were driven to extraordinary efforts. There's a certain drive involved with this. I think you have a feeling that you have to beat your competitor, and the only way you can do that is by working twice as hard or running twice as fast. So we did.

Hughes: Yes, you did. [laughs] How tight a rein were you keeping on people in your laboratory?

Boyer: I was never one to micro-manage. In those days, I would spend a lot of time talking to people about what they were doing, and we'd go over results. We would have lab meetings to talk about problems and organization of the lab.

Hughes: Were they regularly scheduled?

Boyer: I can't remember; I think they were at one point. I can't remember much about the timetable for that sort of thing. But every day, you were always talking about the experiments to be done.

##

Hughes: Was communication stressed in other laboratories, too?

Boyer: Yes.

Hughes: Is this characteristic of molecular biology in general, or is this a UCSF attribute?

Boyer: I think it's fairly characteristic of most universities and research institutions. I think it's the fuel that feeds the engine--the interaction and the communication.

Hughes: At many levels.

Boyer: Yes.

Hughes: But beginning with the laboratory group itself?

Boyer: Yes.

## Key Technologies for Biotechnology

Hughes: Well, are there technological developments that were critical in the recombinant work? You've alluded to some of them.

Boyer: Well, I believe in some of our other sessions that I've talked about the three key technologies for biotechnology--recombinant DNA, DNA sequencing, and chemical synthesis of DNA. So those were the three key ones in my mind. And then a lot of the other things were improvements in efficiency, opening up some new approaches that didn't exist before. We developed vectors in which you could actually select for a recombinant molecule rather than trying to screen it. And hybridization techniques. It goes on and on.

Hughes: You mentioned in an earlier interview that there were problems working with messenger RNA. I believe you were talking about the period in the mid-1970s.

Boyer: Well, the big problem early on was stability. It's still a problem, but not like it used to be. The sensitivity of recovering recombinant molecules is so efficient and sensitive now that some of those early

problems have gone by the wayside, just by virtue of the fact that the cloning technologies have improved.

Hughes: Was it a matter of messenger RNA breaking down?

Boyer: Yes, once you would open up the cells, there were enzymes that would degrade it very quickly. Axel Ullrich, a postdoc at UC San Francisco, worked out some of those techniques, to very quickly lyse the cells and inactivate the nucleases.

## Safety Measures

Hughes: Did you increase safety measures in the laboratory after Asilomar?

Boyer: I think we always felt we were pretty good microbiologists. I don't think that more than a handful of microbiologists really thought any of this was dangerous. But everybody was willing to comply with the guidelines. If you complied with the guidelines, you would avoid legislation which would have been disastrous. The key thing for the Asilomar conference was to avoid legislation.

Hughes: That possibility was a factor in your testimony and Dr. Rutter's when you were called in front of the Senate, was it not?

Boyer: Yes.

Hughes: At that point, there were several bills in both houses, which of course came to naught, but there was a fear that the pBR322 episode might trigger legislation. Do you remember that being in your mind?

Boyer: Absolutely. I don't think there could have been anything more deadly.

Hughes: That was a pretty universal feeling in the scientific community, was it not?

Boyer: Yes.

Hughes: Scientists didn't want regulation imposed by government?

Boyer: Guidelines are guidelines. They are things you should do. If you don't do them, you don't break any laws. But I think everybody essentially followed them. I immediately had gotten some funds and help from

the Department of Biochemistry to build a containment laboratory where all the experiments could be done, so we had this done very early on, soon after the Asilomar conference.

Hughes: The P-3 lab?

Boyer: Yes.

Hughes: Where did those funds come from?

Boyer: I can't remember. I think either from the department, or we got them from the School of Medicine. Bill always had these mysterious sources of money.

Hughes: Why did the threat of legislation diminish?

Boyer: Passage of time and experience. Nobody ever got sick; nobody ever died. More people died from electrophoresis accidents than they did from recombinant DNA. And I think that's the bottom line.

Hughes: What about the promise of the technology? You were right at the core, showing that this technology really did have benefits for society.

Boyer: Nevertheless, regardless of how many benefits you have, it you have some technology that is going to cause serious health problems, like radiation, toxic chemicals, you don't ignore the proper handling and use of that material. You aren't sloppy just because there are great benefits. It was like a defense attorney's argument, that the promise couldn't be ignored--which it couldn't. But it didn't mean that if there were potential dangers, if there were real dangers, that you should not be aware of them and do something about them.

Working with microorganisms is intrinsically dangerous. If you isolate pathogenic organisms from patients or animals, if you're not careful, you can die very easily. People have. There's no question about it. Several people in Yale's virology laboratory died from Rift Valley fever.

## Boyer's Approach to Science

Hughes: You are known as a fine experimentalist. Can you make any generalization about how you approach a research problem? What sort of steps do you take?

Boyer: I'd have to think about that. My favorite quote for postdocs and students, technicians was, "If you know the question, you know half." Which I didn't originate, but I always thought was a very thoughtful way to go about science. You have to raise the question just right, raise a good question about phenomenology, an idea that you can define ways in which to get an answer.

The other key thing about doing science is to be critical, and not to prejudice yourself. If you have a bias towards the outcome of an experiment, you're setting yourself up for disaster. So I always tried to teach people in my lab to look at an experiment as getting an answer, yes or no. And regardless of whether you got a yes or no, it was very useful information, if you did the experiment right. Now, the key is doing the experiment right. But those were some of the guiding principles that I had.

The amazing thing about science is that you really don't operate in a vacuum. You're always going to your colleagues, your students, your postdocs, and you try out an idea or they try out an idea on you, and you try to find a hole in the approach to the problem, or what we call a control which has been overlooked; you haven't controlled all your variables. So it gets to be a game: How do you convince this person that you've done everything you can do to get a good solid answer, whether it's yes or no? And if you haven't, they'll point it out to you. So you go back and you do it. But that interaction, that constant feedback, is very critical for science.

Hughes: Was that feedback occurring within the lab group on a day-to-day basis?

Boyer: Yes. Absolutely.

Hughes: Who else did you talk with?

Boyer: Oh, whomever you bumped into in the hall. But if you had a technical problem, or you needed equipment, you would go and talk to the person that had the technology. Or if you needed a reagent, you would go borrow some, trade or--

Hughes: And were people pretty good about giving reagents?

Boyer: Some people weren't, but most people were.

Gordon Tomkins was a remarkable man because he was always willing to listen to what you were doing, and he was enthusiastic and excited about it. So you could go to him just to bounce ideas off of him. There were a lot of people like that around.

Hughes: Did he get you thinking in different directions?

Boyer: Oh, absolutely. When he first came to UC, before Stanley Cohen and I got together [1972], we used to talk about restriction enzymes. In those days, there just weren't very many people around interested in them, but Gordon was. He found them fascinating, and so it was fun to talk to him. I can remember just the two of us having a discussion after, I think it was, a biochemistry faculty meeting, and talking about wouldn't it be wonderful if restriction enzymes made staggered breaks, because you could get the sticky ends to recombine.

Hughes: Before the fact?

Boyer: Yes.

Hughes: Can you remember when that might have been?

Boyer: Oh, probably about 1970, '71.

Hughes: That was Janet Mertz's contribution, was it not?

Boyer: Well, sticky ends were known a long time before that, because a number of viruses will generate staggered breaks in defined places, usually at the end of the genome. I can remember when I was at Yale writing my first grant request, talking about the sticky ends of lambda [phage], and different ways you could generate molecules of DNA with sticky ends and put them back together again. That was before restriction enzymes were discovered, but that's what I wanted to do.

So those are some of the things that are important for doing science. I just can't overemphasize the value of interaction. Few scientists today sit down and think of something new on their own. They may have an idea, so that the concept is there, but really to work it out, it's usually a team effort.

Hughes: And then there's the team that's preceded you. Ideas are related to past ideas.

Boyer: Yes. You can only build skyscrapers from starting with the foundation, no question about that.

Hughes: What about the role of luck or serendipity or the irrational elements of science?

Boyer: I think serendipity does play a role, but I can't really think of anything in my own research career which could be characterized as serendipitous. Luck and hard work, being in the right place at the right time--if that's serendipity, then there's a lot of that. Serendipitous usually means that you add the wrong reagent, and something fantastic happens.

## Defining Good Science

Hughes: What about a definition of your idea of good science?

Boyer: Good science? Oh, gosh. I guess good science is repeatable science. If you can repeat the experiments, that would probably be the key. Depends on what you mean by good. Are you talking about major contributions?

Hughes: No, I meant on a routine, day-to-day basis, what does the term "good science" mean? What are the elements?

Boyer: I think first of all it has to be repeatable by people who just read your description of how you did the experiment. Good science would be an experiment or series of experiments which lead to a new question or a new insight. It would have to include something novel, not just a repetition, or a me-too, or a wannabe as a reason for the experiment. We've always seen a lot of that. You have several labs working on a similar project, and both labs will publish a paper within a couple of weeks or months of one another. I guess that has some value in terms of an independent confirmation of a finding.

My criticism of science today is that it's fairly redundant, in the sense that you have the same types of experiments done over and over and over again, but with a different gene, a different system, a different animal. I guess some of us are responsible for that, because it's done with recombinant DNA technology. You see a lot of data gathering,

and it's not too often that you get a synthesis of all of that data which leads to a new understanding of a biological mechanism or phenomenon.

You pick up a journal, and you find you've sort of heard it all before, but there's just a new twist to the story. But sometimes--those twists make a big difference. Newspapers have articles that interest people so that they'll buy more newspapers, and journals exist because they publish papers, and if they don't publish papers, they don't serve their function. They're not going to make any money.

## Writing and Publishing Papers

Hughes: Well, speaking of publication, how good were you at writing up your work?

Boyer: Well, I got better as time went on. Experience is great.

Hughes: Did you have any particular plan of attack?

Boyer: Some papers were a lot easier to write than others. Some you could write in a couple of days; others would take weeks or months. Sometimes you'd start working on the paper, and you'd realize you had to do a couple more experiments. Sometimes that would change the whole nature of the paper.

I can remember a couple of occasions. One was when I was a postdoctoral fellow, and my mentor Ed Adelberg was guiding me through writing my first paper by myself. I was the sole author. His comment was, "Remember, you always have to lead the reader down the garden path," or words to that effect. You have to be very logical and explain things in depth.

Then the other occasion I remember very well is when I wrote probably one of the most personally rewarding papers. I submitted it to the *Journal of Molecular Biology*; it was my first paper in the *Journal of Molecular Biology*. It was reviewed by Gunther Stent, who was the editor-in-chief. Gunther sent me a note saying that I should rewrite certain parts of it, because when he read it, it gave him mental diarrhea. [laughter] He always had a way with words. I didn't think it was that bad, but it was not an easy paper to write.

Writing papers was never easy, but some were written faster than others.

Hughes: What were your criteria for choosing journals to submit a paper to?

Boyer: Several. One was based on subject. One was how quickly you could get it published. Some journals have a little more pizzazz than others; some have a different readership. If you had a dull, technical paper, you'd put it in one journal; if you had something you felt was really exciting, you'd go with another one; if you wanted it fast, to beat the competition, you'd go to another. Numerous criteria.

Hughes: Did you ever have trouble getting a paper published?

Boyer: Yes. I think we always ended up publishing them. If it was a "me-too" paper, like a student had done a lot of work on something, then I'd always make them write up the paper. If they were slow doing it, sometimes they'd get beaten out. So if it was a "me-too" type of paper, you'd go to some obscure journal. [tape interruption]

Self-Assessment

Hughes: I'm wondering how you think of yourself. How do you categorize who you are?

Boyer: Oh, that changes almost every day. [laughter]

Hughes: Well, how about today?

Boyer: I've always taken a great deal of pride in not taking myself too seriously. I know that I was involved in a couple of significant things in the biological sciences and biotechnology. That's all in the past. So I feel a great sense of gratification, and I've been amply rewarded. But I don't dwell on it. I have, as you know, a number of things that I like to do, and I enjoy doing them. They don't include science that much anymore. And I'm not unhappy about not doing science anymore. There is a life after science.

But I try not to take myself too seriously. One of my favorite contemporary authors is Tom Robbins. He wrote *Even Cowgirls Get the Blues* and *Another Roadside Attraction*, which were his earlier works, and very good. But one of his later works is called *Jitterbug Perfume*. It's a fantasy, as most of his works are. The protagonist

in this story travels the world over to find the secret of life, and somewhere in a foreign country he's looking for this person who's supposed to know the secret of life. He never meets up with this person, but he happens to come upon an old dusty farmhouse where this person had lived. So he searches it to see if there were any clues about the secret of life.

He walks in, and the mantelpiece is all covered with dust. There written in the dust are the words, "Lighten up." [laughter] Which he took to mean the secret of life. I've always enjoyed that little piece. So that's about all I have to say.

Hughes: Well, I thank you very much.

Transcribed by Shannon Page
Final Typed by Jessica Stern

TAPE GUIDE--Herbert W. Boyer, Ph.D.


Interview 1: March 18, 1994
- Tape 1, Side A 1
- Tape 1, Side B 10
- Tape 2, Side A
- Tape 2, Side B not recorded 19

Interview 2: March 28, 1994
- Tape 3, Side A 25
- Tape 3, Side B 34
- Tape 4, Side A 42
- Tape 4, Side B 52

Interview 3: April 7, 1994
- Tape 5, Side A 55
- Tape 5, Side B 64
- Tape 6, Side A 74
- Tape 6, Side B not recorded

Interview 4: April 20, 1994
- Tape 7, Side A 84
- Tape 7, Side B 92
- Tape 8, Side A 100
- Tape 8, Side B not recorded

Interview 5: July 22, 1994
- Tape 9, Side A 105
- Tape 9, Side B 121

APPENDIX


A Biographical Information and Bibliography, Herbert W. Boyer 131

B Cartoon from a Slide Courtesy of Stanley N. Cohen 145

C Cloning Diagram from a Slide Courtesy of Stanley N. Cohen 146

D Documents Concerning Potential Biohazards

Singer-Soll Letter, *Science* Magazine, Sept. 21, 1973 147

Berg Letter, *Science* Magazine, July 26, 1974 148

"'Fail-Safe' Plan on Gene Research," *San Francisco Chronicle*, February 28, 1975 149

"Genetic Manipulation: Guidelines Issued," *Nature* Magazine, July 1, 1976 151

E UCSF Biosafety Committee

UCSF News Release on Creation of a Campus Biosafety Committee, October 5, 1976 154

Chancellor's Letter on Events in "Modern Biology," March 16, 1977 156

F Sculptures Depicting the Initial Meeting of Swanson and Boyer in Late 1975, with the Living Originals 159

G UCSF News Release on the pBR322 Incident, September 26, 1977 160

H UCSF News Release on Somatostatin, December 2, 1977 162

I Genentech News Release on Human Insulin, September 6, 1978 166

J UCSF/Industry Relations, Circa 1980 172

K Genentech, Inc.

*Time* Magazine Article, October 20, 1980, on Genentech's Initial Public Offering, 1980 177

"Genentech's Herbert Boyer," *Time* Magazine Cover, March 9, 1981 178

Excerpt from 1981 Genentech Annual Report 179

L Selected Honors

National Medal of Technology, 1989 181

National Medal of Science, 1990 183

INDEX 185

Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
**Genentech, Inc.**
Genentech, Inc.

## HERBERT W. BOYER

### MEMBER, BOARD OF DIRECTORS

Herbert W. Boyer, Ph.D. has served as a director of Genentech, Inc. since he co-founded the company in 1976 with Robert A. Swanson, a venture capitalist. He also was a vice president of the company from 1976 to 1990. A biochemist and genetic engineer, Boyer had demonstrated the usefulness of recombinant DNA technology to economically produce medicines, which laid the groundwork for Genentech's development.

In addition to his role at Genentech, Boyer was a professor at the University of California at San Francisco and an investigator for the Howard Hughes Medical Institute. At the time Genentech was formed, Boyer was a professor of biochemistry and biophysics at the University of California at San Francisco as well as the director of the graduate program in genetics. He has taught in the microbiology department as well.

In 1996, Boyer and Dr. Stanley N. Cohen of Stanford University were awarded the Lemelson-MIT Prize, the world's single largest cash prize for American invention and innovation, for discovering recombinant DNA technology. In 1993, Boyer, along with Cohen, was awarded the prestigious Swiss Helmut Horten Research Award for their pioneering use of research in the use of gene technology in medicine. In 1985, he was elected to the California Inventors Hall of Fame and is an elected member of the National Academy of Sciences. Boyer received the Golden Plate Award from the American Academy of Achievement in 1981 and the Albert Lasker Basic Medical Research Award in 1980. He is a Fellow in the American Academy of Arts and Sciences and received the Industrial Research Institute Achievement Award in 1982. Boyer is on several Editorial Boards of scientific publications and has written or co-written over 100 scientific articles.

Boyer received his bachelor's degree in biology and chemistry in 1958 from St. Vincent College in Pennsylvania. He received his master's and doctorate degrees in 1960 and 1963 respectively, from the University of Pittsburgh.

He is professor emeritus of biochemistry and biophysics, University of California, San Francisco, and chairman of the board, Allergan, Inc., a technology-driven global healthcare company.

7/13/99 # # #

Carol Fox, News Director
Source: Robert Sanders (415) 476-2557

BIOGRAPHICAL INFORMATION
December 1989

## HERBERT WAYNE BOYER, PHD

Genetic engineering pioneer Herbert W. Boyer, PhD, 53, professor of biochemistry at the University of California, San Francisco, co-discovered the techniques of recombinant DNA that led to the current revolution in biology and the boom in biotechnology.

In collaboration with Stanley N. Cohen, MD, of Stanford University, they demonstrated that genetic material from bacteria can be recombined with foreign genes and introduced into other bacteria as hybrid chromosomes.

Boyer joined with venture capitalist Robert Swanson in 1976 to found Genentech, Inc., to bring the fruits of this revolutionary development to the marketplace. Genentech was the first and is still the largest gene splicing firm. Since its founding it has produced and is either testing or currently marketing genetically engineered human insulin, interferon, growth hormone, clotting factors and numerous other biological products.

Today hundreds of biotechnology firms employ the Cohen/Boyer technique or similar techniques to produce drugs, hormones, vaccines and other useful products, and the technique is an invaluable tool in basic research labs throughout the world.

Boyer and Cohen first took a gene from one bacteria and inserted it into another in 1973, but genetic engineering's promise truly became evident the next year, when they took a gene from a higher species--a toad--and put it into bacteria.

In 1976 they and other groups around the world showed that synthetic human genes could be put into bacteria as well, and the next year they succeeded in turning these bacteria into "factories" to produce large quantities of a potentially useful human hormone, somatostatin. This work was done in collaboration with the City of Hope Medical Center in Duarte, California, as was the production in 1978 of human insulin

(more)

from bacterial "factories." This work made possible the inexpensive, large scale production of numerous human proteins like insulin and human growth hormone, as well as vaccines and other medical products.

Boyer was born in Derry, Pennsylvania, near Pittsburgh, on July 10, 1936. He received his undergraduate education at St. Vincent College, Latrobe, Pennsylvania, (BA 1958) and did graduate work in bacteriology at the University of Pittsburgh (MS 1960, PhD 1963). Following post-doctoral work in microbial genetics at Yale University (1963-66), he came to UC-San Francisco in 1966 as an assistant professor of microbiology. He is now a professor of biochemistry at UCSF.

Boyer has received numerous awards and honors, including the National Medal of Technology in 1989 and the prestigious Lasker Award for Basic Medical Research in 1980, both of which he received along with Cohen. The Lasker Award is the highest honor bestowed in the United States for basic and clinical research in medicine. He also is a member of the National Academy of Sciences and the American Academy of Arts and Sciences. He was awarded the V.D. Mattia Award of the Roche Institute of Molecular Biology in 1977, again with Cohen, and the two were elected to the California Inventors Hall of Fame in 1982. Both received the Moet Hennessy-Louis Vuitton Prize in 1988 from France's Institut de la Vie, and the first ever City of Medicine Award from the city of Durham, North Carolina, and Duke University. Boyer also was a Howard Hughes Medical Institute Investigator between 1976 and 1983.

He currently is on the board of directors of Genentech, Inc.

----------(more details below)----------

Boyer's principal research interest has been restriction nucleases--enzymes that cut double-stranded DNA at highly specific sites. More than 100 different nucleases, each specific for a different DNA sequence, have been isolated to date from bacteria, which use them to cut up and destroy foreign genes.

This interest in restriction nucleases dates back to Boyer's graduate student days, when he studied how genes control the process in Escherichia coli, a human intestinal bacterium. He subsequently moved to UCSF as an assistant professor, and in 1969 he and graduate student Robert Yoshimori isolated and purified E. coli RI (Eco RI), at the time a unique restriction nuclease because it turned out to have an unusual property--after cutting the twin strands of DNA, it leaves one strand dangling longer than the other. This "sticky end" readily latches onto a complementary sticky end of another piece of DNA, efficiently joining the two.

Boyer and Cohen both recognized the potential of Eco RI. The sticky ends could help insert foreign genes into strands of DNA by facilitating linkage between two pieces of DNA. Cohen and others had been working towards this end

for some years, hoping to insert genes into small free-floating rings of DNA called plasmids. Plasmids are found in all bacteria and typically contain only a few genes, while the bulk of the other 4000 genes bacteria like E. coli contain are carried in a much larger ring structure. He and his colleagues at Stanford, and researchers elsewhere, had developed a way of inducing bacteria to take up foreign plasmids and accept them as their own, to the extent that they even replicated when the bacteria replicated.

Cohen and Boyer decided to work together, proposing to snip open a plasmid with Eco RI, use the sticky ends to insert a foreign gene, and then securely lock the gene into the plasmid with the enzyme DNA ligase. They then could use Cohen's method to induce bacteria to accept the "recombinant" plasmid.

Boyer and Cohen succeeded in 1973 with the insertion of bacterial genes conferring resistance to antibiotics. Results published that year reported the transfer of genes from salmonella and staphylococcus bacteria to the bacteria E. coli, creating in the recipient bacteria resistance to streptomycin and several other antibiotics.

The era of recombinant DNA truly began the following year, however, when they successfully spliced non-bacterial genes (from the toad Xenopus laevis) into a bacterial plasmid. When taken up by bacteria, the recombinant plasmid replicated as if it were a normal part of the bacteria's genome. This was the first instance of replication and transcription of eukaryotic DNA (i.e. genes from higher organisms) in a bacterium.

The field progressed rapidly following these breakthroughs, but the research also engendered an unprecedented public debate about possible risks in the experimental manipulation of genes. Many scientists participated in these discussions, including Boyer and Cohen. Not long after the successes of 1974, Boyer, Cohen and others joined in calling for the temporary voluntary postponement of recombinant DNA work until the potential hazards had been evaluated. This led to a conference at Asilomar in 1975, in which Boyer participated, and resulted in NIH guidelines for the conduct of such research.

1976 saw the publication by Boyer's group and other groups around the country of major research which, in Boyer's words, took "recombinant DNA technology out of the area of basic science and into the area of practical application." This work demonstrated that chemically synthesized human genes, as distinct from genes pulled out of animals or bacteria, could be inserted into bacteria using plasmids, and the genes could function as natural bacterial genes.

These accomplishments signaled the real possibility of the economical production of scarce, medically useful biological substances.

This possibility was realized sooner than anyone expected, and again Boyer was involved. In December 1977, the first successful production in bacteria of a medically useful hormone--somatostatin--was announced. This was accomplished by Boyer and other scientists at UC-San Francisco and the City of Hope Medical Center in Duarte, California.

The scientific team used recombinant DNA techniques to introduce into bacteria a synthetic gene for somatostatin, which is involved in regulating levels of growth hormone in humans. The bacteria subsequently produced pure biologically-active somatostatin.

This work demonstrated that bacteria could be used safely as "factories" to produce medically needed materials. It also showed that bacteria could produce proteins that, as far as the body could tell, were identical to natural human proteins.

In September, 1978, scientists at Genentech Inc. and the City of Hope, using these techniques, successfully transformed bacteria into "factories" for insulin. This has made possible the inexpensive, large-scale production of insulin chemically identical to natural human insulin.

Boyer has continued his work at UCSF on restriction nucleases, concentrating primarily on the nuclease he discovered in 1969, Eco RI. Before he got side-tracked into exploring the uses of recombinant DNA, he was studying the manner in which Eco RI recognizes and binds to DNA. Now, using these same recombinant DNA techniques, he can pursue this question by actually making genetic changes in the nuclease and studying the effect.

In conjunction with John Rosenberg of the University of Pittsburgh, who determined the structure of the nuclease using x-ray crystallography and subsequently developed a computer model of it, Boyer and his coworkers select sites at which to make point mutations in the gene. The resultant effect on the structure or function of the nuclease gives clues to the function of the area mutated. They have shown, for example, that the structure of DNA is kinked when the nuclease binds.

Boyer's group also is studying the primitive bacterium Halobacterium halobium, using a genetic approach to determine how its purple pigment, bacteriorhodopsin, acts as an ion pump.

###

BIBLIOGRAPHY

1. Boyer, H., Englesberg, E., and Weinberg, R. Direct Selection of L-Arabinose Negative Mutants of *Escherichia coli* Strain B/r1. *Genetics* **47**, 417-425, 1962.

2. Englesberg, E., Anderson, R.L., Weinberg, R., Lee, N., Hoffee, P., Huttenhauer, G., and Boyer, H. L-Arabinose-Sensitive, L-Ribulose 5-Phosphate 4-Epimerase-Deficient Mutants of *Escherichia coli*. *J Bacteriol.* **84**, 137-146, 1962.

3. Boyer, H.W. Genetic Control of Restriction and Modification in *Escherichia coli*. *J. Bacteriol.* **88**, 1652-1660, 1964.

4. Weinberg, R., and Boyer, H.W. Base Analogue Induced Arabinose-Negative Mutants of *Escherichia coli*. *Genetics* **51**, 545-553, 1965.

5. Boyer, H. Conjugation in *Escherichia coli*. *J. Bacteriol.* **91**, 1767 - 1772, 1966.

6. Sesnowitz, S., Adelberg, E., and Boyer, H.W. Proflavin Mutagenesis in Bacteria. *Bact. Proc.*, p. 26, 1966.

7. Boyer, H.W., and Carlton, B.C. Production of Two Proteolytic Enzymes by a Transformable Strain of *Bacillus subtilis*. *Arch. Biochem. Biophys.* **128**, 442-445, 1968.

8. Boyer, H., and Roulland-Dussoix, D. A Complementation Analysis of the Restriction and Modification of DNA in *Escherichia coli*. *J. Mol. Biol* . **41**, 459-472, 1969.

9. Roulland-Dussoix, D., and Boyer, H. The *Escherichia coli* B Restriction Endonuclease. *Biochim Biophys Acta* **195**, 219-229, 1969.

10. Mamelak, L., and Boyer, H.W. Genetic Control of the Secondary Modification of Deoxyribonucleic Acid in *Escherichia coli*. *J. Bacteriol.* **104**, 57-62, 1970.

11. Ford, E., and Boyer, H.W. Degradation of Enteric Bacterial Deoxribonucleic Acid by the *Escherichia coli* B Restriction Endonuclease. *J. Bacteriol.* **104**, 594-595, 1970.

12. Boyer, H.W. DNA Restriction and Modification Mechanisms in Bacteria. In *Ann. Rev. Microbiol.*, vol. **25**. C.E. Clifton (ed.), Annual Reviews, Palo Alto, 1971, p. 153-176.

13. Boyer, H., Scibienski, E., Slocum, H., and Roulland-Dussoix, D. The *In Vitro* Restriction of the Replicative Form of W. T. and Mutant fd Phage DNA. *Virology* **46**, 703-710, 1971.

14. Cleaver, J.E., and Boyer, H.W. Solubility and Dialysis Limits of DNA Oligonucleotides. *Biochim. Biophys. Acta* **262**, 116-124, 1972.

15. Hedgpeth, J., Goodman, H.M., and Boyer, H.W. The DNA Nucleotide Sequence Restricted by the RI Endonuclease. *Proc. Natl. Acad. Sci. USA* **69**, 3448-3452, 1972.

16. Yoshimori, R., Roulland-Dussoix, D., and Boyer, H.W. R Factor-Controlled Restriction and Modification of Deoxribonucleic Acid: Restriction Mutants. *J. Bacteriol.* **112**, 1275-1279, 1972.

17. Slocum, H., and Boyer, H.W. Host Specificity of Salmonella Typhimurium Deoxyribonucleic Acid Restriction and Modification. *J. Bacteriol.* **113**, 724-726, 1973.

18. Boyer, H.W., Chow, L.T., Dugaiczyk, A., Hedgpeth, J., and Goodman, H.M. DNA Substrate Site for the EcoRII Restriction Endonuclease and Modification Methylase. *Nature New Biol.* **244**, 40-43, 1973.

19. Hedgpeth, J., and Boyer, H.W. Hydrolysis of Adenosine Triphosphate Accompanying Interaction Between *Escherichia coli* B Restriction Endonuclease and Unmodified Deoxyribonucleic Acid. *Biochim. Biophys. Acta* **331**, 310-317, 1973.

20. Cohen, S.N., Chang, A.C.Y., Boyer, H.W., and Helling, R.B. Construction of Biologically Functional Bacterial Plasmids *In Vitro*. *Proc. Natl. Acad. Sci. USA* **70**, 3240-3244, 1973.

21. Williams, P.H., Boyer, H.W., and Helinski, D.R. Size and Base Composition of RNA in Supercoiled Plasmid DNA. *Proc. Natl. Acad. USA* **70**, 3744-3748, 1973.

22. Dugaiczyk, A., Hedgpeth, J., Boyer, H.W., and Goodman, H.M. Physical Identity of the SV40 Deoxribonucleic Acid Sequence Recognized by the *Eco*RI Restriction Endonuclease and Modification Methylase. *Biochemistry* **13**, 503-512, 1974.

23. Dugaiczyk, A., Boyer, H.W., and Goodman, H.M. Demethylamination of $N^6$-Methyldeoxyadenosine by Commercial Spleen Phosphodiesterase Preparations. *Biochem Biohys. Res. Comm.* **56**, 641-646, 1974.

24. Morrow, J.F., Cohen, S.N., Chang, A.C.Y., Boyer, H.W., Goodman, H.M., and Helling, R.B. Replication and Transcription of Eukaryotic DNA in *Escherichia coli*. *Proc. Natl. Acad. Sci. USA* **71**, 1743-1747, 1974.

25. Boyer, H.W. Restriction and Modification of DNA: Enzymes and Substrates (Symposium FASEB, April 20, 1973). *Fed Proc.* **33**,1125-1127, 1974.

26. Helling, R.B., Goodman, H.M., and Boyer, H.W. Analysis of Endonuclease R-*Eco*RI Fragments of DNA from Lambdoid Bacteriophages and Other Viruses by Agarose-Gel Electrophoresis. *J. Virol.* **14**, 1235-1244, 1974.

27. Greene, P.J., Betlach, M.C., Goodman, H.M., and Boyer, H.W. The *Eco*RI Restriction Endonulcease. In DNA Replication (Methods in Molecular Biology), R. B. Wickner (ed.), Marcel Dekker, Inc., New York, 1974, 7, p. 87-105.

28. Hershfield, V., Boyer, H.W., Yanofsky, C., Lovett, M.A., and Helinski, D.R. Plasmid ColEl as a Molecular Vehicle for Cloning and Amplification of DNA. *Proc. Natl. Acad. Sci. USA* **71**, 3455-3459, 1974.

29. Godson, N., and Boyer, H. Susceptibility of the dX-Like Phages G4 and Gl4 to R-*Eco*RI Endonuclease. *Virology* **62**, 270-275, 1974.

30. Cohen, S.N., Chang, A.C.Y., Morrow, J.F., Boyer, H.W., Goodman, H.M., Helling, R.B., Chow, L., and Hsu, L. *In Vitro* Construction of Bacterial Plasmid Replicons Containing Procaryotic and Eucaryotic Genes. In *Mechanisms of Virus Disease*, W.S Robinson and C.F. Fox (eds.), W.A. Benjamin, Menlo Park, California, 1974, p. 403-419.

31. Chow, L.T., Boyer, H.W., Tischer, E.G., and Goodman, H.M. Electron Microscopic Mapping of the Attachment Sites on SV40 DNA during Lytic Infection. Cold Spring Harbor Symposium on Quantitative Biology **39**, 109-117, 1974.

32. Roulland-Dussoix, D., Yoshimori, R., Greene, P., Betlach, M., Goodman, H.M., and Boyer, H.W. R Factor-Controlled Restriction and Modification of Deoxyribonucleic Acid. In *Microbiology 1974*. David Schlesinger (ed.), American Society for Microbiology, Washington, D.C., 1975, p. 187-198.

33. Boyer, H.W., Greene, P.J., Meagher, R.B., Betlach, M.C., Russel, D., and Goodman, H.M. The Methylation of DNA as the Biochemical Basis of Host Controlled Modification of DNA in Bacteria. *FEBS Symposium (1974)*. Budapest, Hungary, 1975, v. 34, p. 23-37.

34. Dugaiczyk, A., Boyer, H.W., and Goodman, H.M. Ligation of *Eco*RI Endonuclease-generated DNA Fragments into Linear and Circular Structures. *J. Mol. Biol.* **96**, 171-184, 1975.

35. Greene, P.J., Poonian, M.S., Nussbaum, A.L., Tobias, L., Garfin, D.E., Boyer, H.W., and Goodman, H.M. Restriction and Modification of a Self-Complementary Octanucleotide Containing the *Eco*RI Substrate. *J Mol. Biol.* **99**, 237-261, 1975.

36. Polisky, B., Greene, P., Garfin, D.E., McCarthy, B.J., Goodman, H.M., and Boyer, H.W. Specificity of Substrate Recognition by the *Eco*RI Restriction Endonuclease. *Proc. Natl. Acad. Sci. USA* **72**, Proc. 3310-3314, 1975.

37. Mantei, N., Boyer, H.W., and Goodman, H.M. Mapping Simian Virus 40 Mutants by Construction of Partial Heterozygotes. *J. Virology* **16**, 754-757, 1975.

38. Garfin, D.E., Boyer, H.W., and Goodman, H.M. Sequences Spanning the *Eco*RI Substrate Site. *Nucleic Acids Research* **2**, 1851-1865, 1975.

39. Bulkacz, J., Roulland-Dussoix, D., Boyer, H.W. Deoxyribonucleic Acid Modification by Intermediate-Type Modification Mutants of *Escherichia coli* K-12 and B. *J. Bacteriol.* **124**, 1395-1402, 1975.

40. Brown, W.M., Watson, R.M., Vinograd, J., Tait, K.M., Boyer, H.W., The Structures and Fidelity of Replication of Mouse Mitochondrial DNA-pSC101 *Eco*RI Recombinant Plasmids Grown in *E. coli* K12. *Cell* **7** 517-530, 1976.

41. Betlach, M., Hershfield, V., Chow, L., Brown, W., Goodman, H.M., and Boyer, H.W. A Restriction Endonuclease Analysis of the Bacterial Plamid Controlling the *Eco*RI Restriction and Modification of DNA. (FASEB Symposium, April 1974) *Fed. Proc.* **35**, 2037-2043, 1976.

42. Hershfield, V., Boyer, H.W., Chow, L., and Helinski, D. Characterization of a Mini-ColEl Plasmid. *J. Bacteriol.* **126**, 447-453, 1976.

43. Boyer, H.W., Tait, R.C., McCarthy, B.J., and Goodman, H.M. Cloning of Eucaryotic DNA as an Approach to the Analysis of Chromosome Structure and Function. In *Genetic Improvement of Seed Proteins,* Natl. Acad. Sci., 1976.

44. So, M., Boyer, H.W., Betlach, M., and Falkow, S. Molecular Cloning of an *Escherichia coli* Plasmid Determinant That Encodes for the Production of Heat-Stable Enterotoxin. *J. Bacteriol.,* **128**, 463-472, 1976.

45. Heyneker, H.L., Shine, J., Goodman, H.M., Boyer, H.W., Rosenberg, J., Dickerson, R.E., Narang, S.A., Itakura, K., Lin, S., and Riggs, A.D. Synthetic *Lac* Operator DNA is Functional *In Vivo*. *Nature* **263**, 748-752, 1976.

46. Tait, R.C., Meagher, R.B., Goodman, H.M., and Boyer, H.W. The Production of Proteins by Bacterial Plasmids Containing Eucaryotic DNA Fragments. In *Molecular Mechanisms in the Control of Gene Expression* (ICN-UCLA Symposia on Molecular and Cellular Biology, Vol. V), D. P. Nierlich, W. J. Rutter, and C. F. Fox (eds.), Academic Press, New York, N.Y., 1976, p. 507-512.

47. Brown, W.M., Watson, R.M., Vinograd, J., Tait, K.M., Boyer, H.W., and Goodman, H.M. The Fidelity of Replication of Mouse Mitochondrial DNA-pSC101 Recombinant Plasmids Grown in *E. coli* K12. In *Molecular Mechanisms in the Control of Gene Expression* (ICN-UCLA Symposia on Molecular and Cellular Biology, Vol. V), D. P. Nierlich, W. J. Rutter, and C. F. Fox (eds.), Academic Press, New York, N. Y., 1976, p. 487-493.

48. Rodriguez, R.L., Bolivar, F., Goodman, H.M., Boyer, H.W., and Betlach, M. Construction and Characterization of Cloning Vehicles. In *Molecular Mechanisms in the Control of Gene Expression* (ICN-UCLA Symposia on Molecular and Cellular Biology, Vol. V), D. P. Nierlich, W. J. Rutter, and C. F. Fox (eds.), Academic Press, New York, N. Y., 1976, p. 471-477.

49. Dugaiczyk, A., Tischer, E.G., Nasser, D., Boyer, H.W., McCarthy, B.J., and Goodman, H.M. Cloning of Drosophila Melanogaster *Eco*RI DNA Fragments. In *Molecular Mechanisms in the Control of Gene Expression* (ICN-UCLA Symposia on Molecular and Cellular Biology, Vol. V), D. P. Nierlich, W. J. Rutter, and C. F. Fox (eds.), Academic Press, New York, N. Y., 1976, p. 543-552.

50. Goodman, H.M., Greene, P.J., Garfin, D.E., and Boyer, H.W. DNA Site Recognition by the *Eco*RI Restriction Endonuclease and Modification Methylase. In *Nucleic Acid-Protein Recognition,* P & S Biomedical Sciences Symposia, Nucleic Acid-Protein Recognition, H.J. Vogel (ed.), Academic Press, N. Y. 1977, p. 239-259.

51. Meagher, R.B., Tait, R.C., Betlach, M., and Boyer, H.W. Protein Expression in *E. coli* Minicells by Recombinant Plasmids. *Cell* **10**, 521-536, 1977.

52. Scheller, R.H., Dickerson, R.E., Boyer, H.W., Riggs, A.D. and Itakura, K. Chemical Synthesis of Restriction Enzyme Recognition Sites Useful for Cloning. *Science* **196**, 177-180, 1977.

53. Tait, R.C., Rodriguez, R.L., and Boyer, H.W. Altered Tetracycline Resistance in pSC101 Recombinant Plasmids. *Molec. Gen. Genet.* **151**, 327-331, 1977.

54. Sugino, A., Goodman, H.M., Heyneker, H.L., Shine, J., Boyer, H.W., and Cozzarelli, N.R. Interaction of Bacteriophage T4 RNA and DNA Ligases in the Joining of Duplex DNA at Base-paired Ends. *J. Biol. Chem.* **252**, 3987-3994, 1977.

55. Boyer, H.W., Betlach, M., Bolivar, R., Rodriguez, R.L., Heyneker, H.L., Shine, J., and Goodman, H.M. The Construction of Molecular Cloning Vehicles. In *Recombinant Molecules: Impact on Science and Society*, R.F. Beers and E.G. Bassett (eds.), Raven Press, New York, 1977, pp. 9-20.

56. Rodriguez, R.L., Tait, R., Shine, J., Bolivar, F., Heyneker, H.L., Betlach, M., and Boyer, H.W. Characterization of Tetracycline and Ampicillin Resistant Plasmid Cloning Vehicles. In *Molecular Cloning of Recombinant DNA*, vol. 13, Academic Press, New York, 1977, pp.73-84.

57. Itakura, K., Crea, R., Hirose, T., Riggs, A.D., Heyneker, H.L., Bolivar, F., and Boyer, H.W. Expression in *Escherichia coli* of a Chemically Synthesized Gene for the Hormone Somatostatin. *Science* **198**, 1056-1063, 1977.

58. Bolivar, F., Rodriguez, R.L., Betlach, M.C., and Boyer, H.W. Construction and Characterization of New Cloning Vehicles: I. Ampicillin resistant derivatives of the plasmid pMB9. *Gene* **2**, 75-93, 1977.

59. Bolivar, F., Rodriguez, R.L., Greene, P.J., Betlach, M.C., Heyneker, H.L., Boyer, H.W., Crosa, J.H., and Falkow, S. Construction and Characterization of New Cloning Vehicles: II. A multipurpose cloning system. *Gene* **2**, 95-113, 1977.

60. Meagher, R.B., Shepherd, R.J., and Boyer, H.W. The Structure of Cauliflower Mosaic Virus: I. A restriction endonuclease map of cauliflower mosaic virus DNA. *Virology* **80**, 363-375, 1977.

61. Bolivar, F., Betlach, M.C., Heyneker, H.L., Shine, J., Rodriguez, R.L., and Boyer, H.W. Origin of Replication of pBR345 Plasmid DNA. *Proc. Natl Acad. Sci. USA* **74**, 5265- 5269, 1977.

62. Poon, R., Neumann, K.H., Boyer, H.W., Dozy, A.M., Temple, G.F., Chang, J.C., Kan, Y.W. Cloning Human Globin Genes in Bacterial Plasmid. *Blood* **50**, 124, 1977.

63. Tait, R.C., and Boyer, H.W. On the Nature of Tetracycline Resistance Controlled by the Plasmid pSCl0l. *Cell* **13**, 73-81, 1978.

64. Tait, R.C., Heyneker, H.L., Rodriguez, R.L., Bolivar, F., Covarrubias, A., Betlach, M., and Boyer, H.W. Tetracycline Resistance Conferred by pSCl0l, pMB9, and Their Derivatives. In *Microbiology 1978* ASM, Washington, D.C., 1978, pp. 174-176.

65. Fouts, D.L., Wolstenholme, D.R., and Boyer, H.W. Heterogeneity in Sensitivity to Cleavage by the Restriction Endonucleases *Eco*RI and*Hind*III of Circular Kinetoplast DNA Molecules of *Crithidia acanthocephali.. J. Cell Biol.* **79**, 329- 341, 1978.

66. Rosenberg, J.M., Dickerson, R.E., Greene, P.J. and Boyer, H.W. Preliminary X-ray Diffraction Analysis of Crystalline *Eco*RI Endonuclease. *J. Mol. Biol.* **122**, 241-245, 1978.

67. Greene, P.J., Heyneker, H.L., Bolivar, F., Rodriguez, R.L., Betlach, M.C., Covarrubias, A.A., Backman, K., Russel, D.J., Tait, R., and Boyer, H.W. A General Method for the Purification of Restriction Enzymes. *Nucleic Acids Res.* **5**, 2373-2380, 1978.

68. Tait, R.C., and Boyer, H.W. Restriction Endonuclease Mapping of pSC101 and pMB9. *Molec. Gen. Genet.* **164**, 285-288, 1978.

69. Poon, R., Kan, Y.W., and Boyer, H.W. Sequence of the 3'-noncoding and Adjacent Coding Regions of Human q-globin mRNA. *Nucleic Acids Res.* **5**, 4625-1978.

70. Backman, K., Betlach, M., Boyer, H.W., and Yanofsky, S. Genetic and Physical Studies on the Replication of ColEl-type Plasmids. *Cold Spring Harbor Symp. Quant. Biol.* **43**, 1979, pp. 69-76.

71. Rodriguez, R.L., West, R.W., Heyneker, H.L., Bolivar, F., and Boyer, H.W. Characterizing Wild-type and Mutant Promoters of the Tetracycline Resistance Gene in pBR313. *Nucleic Acids Res.* **6**, 3267-3287, 1979.

72. Boyer, H.W. The Age of Molecular Biology. *APLA Quarterly Journal* **7**, 185-189, 1979.

73. Joseph-Bravo, P., Charli, J.L., Sherman, T., Boyer, H., Bolivar, F., and McKelvy, J.F. Identification of a Putative Hypothalamic mRNA Coding for Somatostatin and its Product in Cell-free Translation. *Biochem. Biophys. Res. Commun.* **94**, 1004-1012, 1980.

74. Dijkema, R., Dekker, M.M., van Ormondt, H., de Waard, A., Maat, J., and Boyer, H. Gene Organization of the Transforming Region of Weakly Oncogenic Adenovirus Type 7: the Ela region. *Gene* **12**, 287-299, 1980.

75. Greene, P.J., Gupta, M., Boyer, H.W., Brown, W.E., and Rosenberg, J.M. Sequence Analysis of the DNA Encoding the *Eco*RI Endonuclease and Methylase. *J. Biol. Chem.* **256**, 2143-2153, 1981.

76. Rosenberg, J.M., Boyer, H.W., and Greene, P. The Structure and Function of the *Eco*RI Restriction Endonuclease. In: *Gene Amplification and Analysis, Vol.* **1** *Restriction Endonucleases,* J.G. Chirikjian, ed., Elsevier-North Holland, New York, 1981, pp. 131-164.

77. Dijkema, R., Maat, J., Dekker, B.M.M., van Ormondt, H., and Boyer, H.W. The Gene for Polypeptide IX of Human Adenovirus Type 7. *Gene* **13**, 375-385, 1981.

78. Betlach, M., Pfeifer, F., Friedman, J., and Boyer, H.W. Bacterio-opsin Mutants of H. halobium. *Proc. Natl. Acad. Sci. USA* 80, 1416-1420, 1983.

79. Pfeifer, F., Betlach, M., Martienssen, R., Friedman, J., and Boyer, H.W. Transposable Elements of *Halobacterium halobium. Molec. Gen. Genet.* **191**, 182-188, 1983.

80. Jen-Jacobson, L., Kurpiewski, M., Lesser, D., Grable, J., Boyer, H.W., Rosenberg, J.M., and Greene, P.J. Coordinate Ion-Pair Formation Between *Eco*RI Endonuclease and DNA. *J. Biol. Chem.* **258**, 14638-14646, 1983.

81. Backman, K., and Boyer, H.W. Tetracycline Resistance Determined by pBR322 is Mediated by One Polypeptide. *Gene* **26**, 197-203, 1983.

82. Pfeifer, F., Friedman, J., Boyer, H.W., and Betlach, M. Characterization of Insertions Affecting the Expression of the Bacterio-opsin Gene in *Halobacterium halobium.*. *Nucleic Acids Res.* **12**, 2489-2497, 1984.

83. Frederick, C.A., Grable, J., Melia, M., Samudzi, C., Jen-Jacobson, L., Wang, B.-C., Greene, P., Boyer, H.W., and Rosenberg, J.M. Kinked DNA in crystalline complex with *Eco*RI endonuclease. *Nature* **309**, 327-331, 1984.

84. Grable, J., Frederick, C.A., Samudzi, C., Jen-Jacobson, L., Lesser, D., Greene, P., Boyer, H.W., Itakura, K., and Rosenberg, J.M. Two-Fold Symmetry of Crystalline DNA-*Eco*RI Endonuclease Recognition Complexes. *J. Biomolec. Struct. & Dynamics* **1**, 1149-1160, 1984.

85. Betlach, M., Friedman, F., Boyer, H.W., and Pfeifer, F. Characterization of a Halobacterial Gene Affecting Bacterio-opsin Gene Expression. *Nucleic Acids Res.* **12**, 7949-7959, 1984.

86. McClarin, J.A., Frederick, C.A., Grable, J., Samudzi, D.T., Wang, B-C, Greene, P., Boyer, H.W., and Rosenberg, J.M. Structural Studies of a DNA-*Eco*RI Endonuclease Recognition Complex. *Proceedings From the Fourth Conversation in Biomolecular Stereodynamics,* 1985.

87. Pfeifer, F.A., Boyer, H.W., and Betlach, M.C. Restoration of Bacterio-opsin Gene Expression in a Revertant of *Halobacterium halobium. J. Bact.* **164**, 414-420, 1985.

88. Betlach, M.C., Leong, D., and Boyer, H.W. 1986. Bacterio-Opsin Gene Expression in *Halobacterium halobium. System. Appl. Microbiol.* 7, 83-89, 1986.

89. Betlach, M.C., Leong, D., Pfeifer, F., and Boyer, H.W. 1986. Bacterio-opsin Gene Expression in *Halobacterium halobium.* In: *Archaebacteria*, O. Kandler (ed.). Fisher Verlag, Stuttgart. In Press.

90. Betlach, M., Leong, D., Pfeifer, F., and Boyer, H.W. 1986. Bacterio-opsin Gene Expression in *Halobacterium halobium.* In: *Microbiology 1986*, S. Silver (ed.). American Society for Microbiology, 363-369.

91. Betlach, M., Leong, D., and Boyer, H. 1986. *E. Coli* Expression Vectors for Bacterio-opsin. *Nauka* (Russian Journal), In Press.

92. Kuhn, I., Stephenson, F.H., Boyer, H.W., and Greene, P.J. 1986. Positive Selection Vectors Utilizing Lethality of the *Eco*RI Endonuclease. *Gene* **42**, 253-263.

93. McClarin, J.A., Frederick, C.A., Wang, B-C., Greene, P., Boyer, H.W., Grable, J., and Rosenberg, J.M. 1986. Structure of the DNA-*Eco*RI Endonuclease Recognition Complex at 3 Å Resolution. *Science* **234**, 1526-1541.

94. Betlach, M., Leong, D., and Boyer, H. 1987. *E. coli* Expression Vectors for Bacterio-opsin. *Proceedings from the Second International Conference on Retinal Proteins*. VNU Science Press, The Netherlands, pp. 317-331.

95. Rosenberg, J.M., McClarin, J.A., Frederick, C.A., Wang, B-C., Grable, J., Boyer, H.W. and Greene, P. 1987. Structure and Recognition Mechanism of *Eco*RI Endonuclease. *Trends in Biochemical Sciences (TIBS)* **12**, #10, 395-398.

96. Rosenberg, J.M., McClarin, J.A., Frederick, C.A., Grable, J., Boyer, H.W. and Greene, P.J. 1987 Structure and Function of the *Eco*RI Restriction Endonuclease. In: *Gene Amplication and Analysis,* Vol. 5, *Restriction Endonucleases and Methylases,* J.G. Chirikjian, ed., Elsevier Science Publishing Co., Inc., New York, pp. 119-147.

97. Rosenberg, J.M., McClarin, J.A., Frederick, C.A., Wang, B-C., Boyer, H.W., Grable, J. and Greene, P. 1987 The Structure and Function of *Eco*RI Endonuclease. In: *Biological Organization: Macromolecular Interactions at High Resolution*, R.M. Burnett and H.J. Vogel, eds., Academic Press, Inc., Orlando, pp. 11-43.

98. Yanofsky, S.D., Love, R., McClarin, J.A., Rosenberg, J.M., Boyer, H.W. and Greene, P.J. 1987 Clustering of Null Mutations in the *Eco*RI Endonuclease. *Proteins: Structure, Function and Genetics* , Vol 2, #4, 273-282.

99. Greene, P.J., Yanofsky, S., Reich, N., Day, J., Hager, P., Boyer, H.W., McClarin, J.A., Frederick, C.A., Wang, B-C., Grable, J., Love, R., and Rosenberg., J.M. *Protein Structure, Folding and Design.* UCLA Symposia on Molecular and Cellular Biology, New Series, Vol. 69. Dale Oxender, ed., Alan R. Liss, Inc., New York, 1987.

100. Greene, P.J., Ballard, B.T., Stephenson, F., Kohr, W.J., Rodriguez, H., Rosenberg, J.M. and Boyer, H.W. 1988 Purification and Characterization of the Restriction Endonuclease *Rsr*I, an Isoschizomer of *Eco*RI. Gene **68**, 43-52.

101. Harley, C.B., Lawrie, J., Betlach, M., Crea, R., Boyer, H.W. and Hedgpeth, J. Transcription Initiation at the *tet* promoter and Effect of Mutations. 1988. *Nucleic Acids Research* **16** #15, 7269-7285.

102. Leong, D., Pfeifer, F., Boyer, H. and Betlach, M. 1988. Characterization of a putative second gene involved in bacterio-opsin gene expression in a halophilic archaebacterium. J. Bacteriol. **170**, 4903-4909.

103. Leong, D., Boyer, H. and Betlach. 1988. Transcriptional analyses of genes involved in bacterio-opsin gene expression in a halophilic archaebacterium. J. Bacteriol. **170**, 4910-4915.

104. Needels, M.C., Fried, S.R., Love, R., Rosenberg, J.M., Boyer, H.W., and Greene, P.J. Determinants of *Eco*RI endonuclease sequence discrimination. PNAS.

105. Reich, N., Hager, P., Day, J., Boyer, H.W., Rosenberg, J., and Greene, P.J. Probing Glutamic Acid-DNA Interactions in the *Eco*RI Endonuclease Using Aspartic Acid and Glutamine Replacements. Submitted to J.B.C.

106. Ballard, J., Stephenson, F., Boyer, H.W., Rosenberg, J., and Greene, P.J. Sequence Analysis of the *Rsr*I endonuclease. Gene, in press.

107. Hager, P., Reich, N., Day, J., Greene, P.J., and Rosenberg, J. Sequence Discrimination by EcoRI Endonuclease is Enhanced by Review of the Nicked DNA Intermediate. In preparation.

RELATED PAPERS FROM BOYER LAB

Pfeifer, F. and Betlach, M. 1985 Genome organization in *Halobacterium halobium*: A 70 kb island of more (AT) rich DNA in the chromosome. *Mol. Gen. Genet.* 198: 449-455.

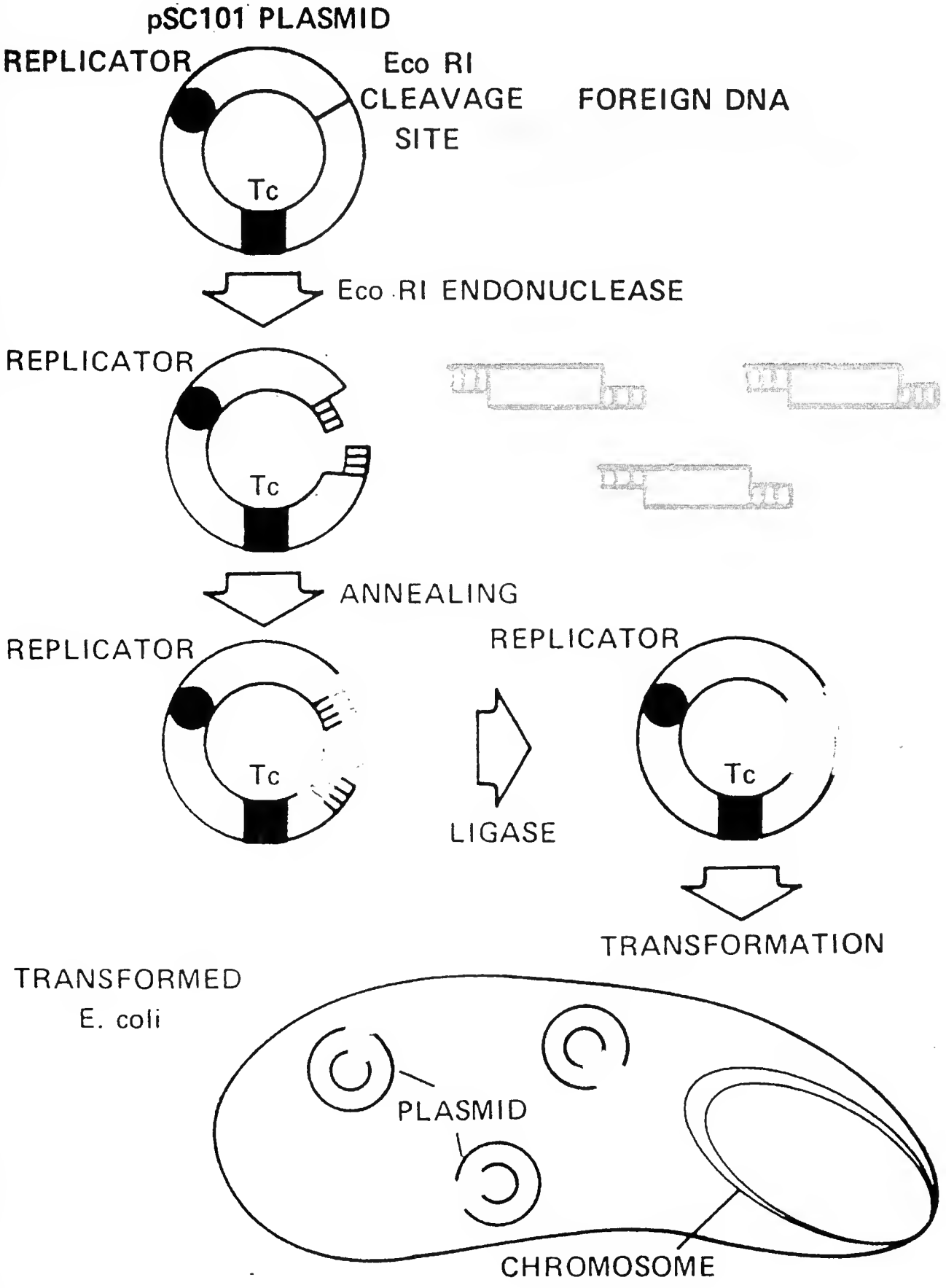
Rosenberg, J.M., Wang, B-C., Frederick, C.A., Reich, N., Greene, P.J., Grable, J. and McClarin, J. 1987 Development of a Protein Design Strategy for *Eco*RI Endonuclease. In: *Protein Engineering,* D.L. Oxender and C.F. Fox, eds. Alan R. Liss, New York, pp. 237-251.

Betlach, M.C., Shand, R.F., Leong, D.M. 1989 Regulation of the bacterio-opsin gene of a halophilic archaebacterium. Can. J. Microbiol. 35: 134-140.


Cartoon of the November 1972 discussion in a Honolulu delicatessen. Stanley Cohen and Herbert Boyer agreed to collaborate in experiments resulting in recombinant DNA.

Copy from a slide courtesy of Stanley N. Cohen, MD

# MOLECULAR CLONING PROCEDURE



LETTERS

## Guidelines for DNA Hybrid Molecules

Those in attendance at the 1973 Gordon Conference on Nucleic Acids voted to send the following letter to Philip Handler, president of the National Academy of Sciences, and to John R. Hogness, president of the National Institute of Medicine. A majority also desired to publicize the letter more widely.

We are writing to you, on behalf of a number of scientists, to communicate a matter of deep concern. Several of the scientific reports presented at this year's Gordon Research Conference on Nucleic Acids (June 11–15, 1973, New Hampton, New Hampshire) indicated that we presently have the technical ability to join together, covalently, DNA molecules from diverse sources. Scientific developments over the past two years make it both reasonable and convenient to generate overlapping sequence homologies at the termini of different DNA molecules. The sequence homologies can then be used to combine the molecules by Watson-Crick hydrogen bonding. Application of existing methods permits subsequent covalent linkage of such molecules. This technique could be used, for example, to combine DNA from animal viruses with bacterial DNA, or DNA's of different viral origin might be so joined. In this way new kinds of hybrid plasmids or viruses, with biological activity of unpredictable nature, may eventually be created. These experiments offer exciting and interesting potential both for advancing knowledge of fundamental biological processes and for alleviation of human health problems.

Certain such hybrid molecules may prove hazardous to laboratory workers and to the public. Although no hazard has yet been established, prudence suggests that the potential hazard be seriously considered.

A majority of those attending the Conference voted to communicate their concern in this matter to you and to the President of the Institute of Medicine (to whom this letter is also being sent). The conferees suggested that the Academies establish a study committee to consider this problem and to recommend specific actions or guidelines, should that seem appropriate. Related problems such as the risks involved in current large-scale preparation of animal viruses might also be considered.

MAXINE SINGER
*Room 9N-119, Building 10,*
*National Institutes of Health,*
*Bethesda, Maryland 20014*

DIETER SOLL
*Department of Molecular Biophysics*
*and Biochemistry,*
*Yale University,*
*New Haven, Connecticut 06520*

Science Magazine, September 21, 1973

LETTERS

## Potential Biohazards of Recombinant DNA Molecules

Recent advances in techniques for the isolation and rejoining of segments of DNA now permit construction of biologically active recombinant DNA molecules in vitro. For example, DNA restriction endonucleases, which generate DNA fragments containing cohesive ends especially suitable for rejoining, have been used to create new types of biologically functional bacterial plasmids carrying antibiotic resistance markers (*1*) and to link *Xenopus laevis* ribosomal DNA to DNA from a bacterial plasmid. This latter recombinant plasmid has been shown to replicate stably in *Escherichia coli* where it synthesizes RNA that is complementary to *X. laevis* ribsomal DNA (*2*). Similarly, segments of *Drosophila* chromosomal DNA have been incorporated into both plasmid and bacteriophage DNA's to yield hybrid molecules that can infect and replicate in *E. coli* (*3*).

Several groups of scientists are now planning to use this technology to create recombinant DNA's from a variety of other viral, animal, and bacterial sources. Although such experiments are likely to facilitate the solution of important theoretical and practical biological problems, they would also result in the creation of novel types of infectious DNA elements whose biological properties cannot be completely predicted in advance.

There is serious concern that some of these artificial recombinant DNA molecules could prove biologically hazardous. One potential hazard in current experiments derives from the need to use a bacterium like *E. coli* to clone the recombinant DNA molecules and to amplify their number. Strains of *E. coli* commonly reside in the human intestinal tract, and they are capable of exchanging genetic information with other types of bacteria, some of which are pathogenic to man. Thus, new DNA elements introduced into *E. coli* might possibly become widely disseminated among human, bacterial, plant, or animal populations with unpredictable effects.

Concern for these emerging capabilities was raised by scientists attending the 1973 Gordon Research Conference on Nucleic Acids (*4*), who requested that the National Academy of Sciences give consideration to these matters. The undersigned members of a committee, acting on behalf of and with the endorsement of the Assembly of Life Sciences of the National Research Council on this matter, propose the following recommendations.

First, and most important, that until the potential hazards of such recombinant DNA molecules have been better evaluated or until adequate methods are developed for preventing their spread, scientists throughout the world join with the members of this committee in voluntarily deferring the following types of experiments.

► *Type 1*: Construction of new, autonomously replicating bacterial plasmids that might result in the introduction of genetic determinants for antibiotic resistance or bacterial toxin formation into bacterial strains that do not at present carry such determinants; or construction of new bacterial plasmids containing combinations of resistance to clinically useful antibiotics unless plasmids containing such combinations of antibiotic resistance determinants already exist in nature.

► *Type 2*: Linkage of all or segments of the DNA's from oncogenic or other animal viruses to autonomously replicating DNA elements such as bacterial plasmids or other viral DNA's. Such recombinant DNA molecules might be more easily disseminated to bacterial populations in humans and other species, and thus possibly increase the incidence of cancer or other diseases.

Second, plans to link fragments of animal DNA's to bacterial plasmid DNA or bacteriophage DNA should be carefully weighed in light of the fact that many types of animal cell DNA's contain sequences common to RNA tumor viruses. Since joining of any foreign DNA to a DNA replication system creates new recombinant DNA molecules whose biological properties cannot be predicted with certainty, such experiments should not be undertaken lightly.

Third, the director of the National Institutes of Health is requested to give immediate consideration to establishing an advisory committee charged with (i) overseeing an experimental program to evaluate the potential biological and ecological hazards of the above types of recombinant DNA molecules; (ii) developing procedures which will minimize the spread of such molecules within human and other populations; and (iii) devising guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.

Fourth, an international meeting of involved scientists from all over the world should be convened early in the coming year to review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules.

The above recommendations are made with the realization (i) that our concern is based on judgments of potential rather than demonstrated risk since there are few available experimental data on the hazards of such DNA molecules and (ii) that adherence to our major recommendations will entail postponement or possibly abandonment of certain types of scientifically worthwhile experiments. Moreover, we are aware of many theoretical and practical difficulties involved in evaluating the human hazards of such recombinant DNA molecules. Nonetheless, our concern for the possible unfortunate consequences of indiscriminate application of these techniques motivates us to urge all scientists working in this area to join us in agreeing not to initiate experiments of types 1 and 2 above until attempts have been made to evaluate the hazards and some resolution of the outstanding questions has been achieved.

PAUL BERG, *Chairman*
DAVID BALTIMORE
HERBERT W. BOYER
STANLEY N. COHEN
RONALD W. DAVIS
DAVID S. HOGNESS
DANIEL NATHANS
RICHARD ROBLIN
JAMES D. WATSON
SHERMAN WEISSMAN
NORTON D. ZINDER
*Committee on Recombinant DNA Molecules Assembly of Life Sciences, National Research Council, National Academy of Sciences, Washington, D.C. 20418*

### References and Notes

1. S. N. Cohen, A. C. Y. Chang, H. Boyer, R. B. Helling, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 3240 (1973); A. C. Y. Chang and S. N. Cohen, *ibid.*, **71**, 1030 (1974).
2. J. F. Morrow, S. N. Cohen, A. C. Y. Chang, H. Boyer, H. M. Goodman, R. B. Helling, *ibid.*, in press.
3. D. S. Hogness, unpublished results; R. W. Davis, unpublished results; H. W. Boyer, unpublished results.
4. M. Singer and D. Soll, *Science* **181**, 1114 (1973).

San Francisco Chronicle ★★★ Fri., Feb. 28, 1975

# 'Fail-Safe' Plan On Gene Research

By David Perlman
Science Correspondent

Pacific Grove

An international working group of biologists agreed yesterday on a historic set of safety principles to govern their research into the promising but potentially hazardous area of genetic engineering.

Drs. Boyer and Berg joined in a call for a self-imposed halt to potentially hazardous research

The guidelines they set for themselves will permit them to resume many experiments they had voluntarily halted last July — but to resume them under new and stringent safeguards.

A few experiments with the most dangerously infectious types of viruses will continue to be deferred until the scientists themselves are far more certain that the hazards can be completely contained.

The nature of the safeguards the scientists recommended are in themselves remarkable and unprecedented. They call for the deliberate creation of new man-made microbes that can thrive in the laboratory but will die instantly should they accidentally escape.

The biologists will use these "self-destructing" microbes for any significantly dangerous genetic experiments from now on to prevent the germs from infecting people, animals or even plants in the world at large.

And several teams of co-

Back Page Col. 3

San Francisco Chronicle, February 28, 1974: A1

# GENETIC RESEARCH

DR. SIDNEY BRENNER
British biologist

DR. A. A BAYEV
Soviet scientist

STANFORD'S DR. STANLEY COHEN
He wanted to balance hazards against benefits

From Page 1

operating scientists agreed here that they can create the first of these "safe" experimental germs swiftly — within the next few days or weeks.

The major experiments under consideration here are part of an explosive new area of genetics that, as the scientists declared, "promises to revolutionize molecular biology," and create a "significant impact" in future benefits for mankind.

The work involves creating what the scientists themselves term "novel biotypes" — in other words, new forms of microscopic life made by combining the genes of widely different organisms. These genes could be dangerous, and could, for example, cause virulent infectious diseases, or spread unwanted resistance to anti-biotics among the population.

But there is little question among the 150 eminent biologists who gathered here for four days and nights of intensive and at times vigorous debate, that the benefits will be imposing.

First is a great increase in fundamental scientific knowledge about the intimate mechanisms of heredity — knowledge to help unravel the precise chemical groupings that govern all the inherited characteristics of living things.

Beyond that is the imminent prospect of more practical results:

Manipulating the genes of bacteria to make them grow huge quantities of cheap anti-biotics, vaccines or medically-needed hormones, like insulin, is one example.

Creating genetically altered bacteria that can thrive at the roots of food plants to manufacture fertilizer from the nitrogen of the air, is another.

Probing the puzzles of cancer viruses — and perhaps even solving them — is a third, more remote, promise.

All these prospects stem from research that climaxed in the late 1960s when teams of scientists — one headed by Dr. Herbert Boyer, of the University of California at San Francisco — first discovered a class of enzymes that could snip apart the giant molecules that formed the genes of all living cells.

These so-called "restriction enzymes" were later used by other scientists to transfer segments of genetic material from one species of organism into the genes of other, unrelated species.

One such set of experiments, performed at Stanford in 1972 by Dr. Stanley Cohen and his colleagues, transferred the hereditary ability to resist antibiotics from one set of common bacteria to another.

That same year, still another group, headed by Dr. Paul Berg, of Stanford, used similar enzymes to insert genes from a monkey virus into the genetic material of a bacteria called Escherichia coli, which normally lives in the human digestive tract.

They wanted the worldwide community of biologists to weigh the unknown hazards of this work against its benefits, and to design safety measures to minimize the dangers to the public and the global environment.

They classified experiments according to their degree of potential hazard. They recommended rigorous, and in many cases highly-expensive, modification of laboratories in order to keep genetically altered experimental germs from escaping.

And they set standards for matching the hazards and the safety measures according to a graded scale.

They also urged biologists and geneticists in every country to develop within their own traditions the processes by which safety controls can be self-imposed or regulated without blocking further research.

Experiments like these impelled Berg, Cohen and Boyer and several other scientists to call on their colleagues last summer for an unprecedented self-imposed halt in much of this research.

The meeting that ended here yesterday under Berg's chairmanship was the first major step toward that goal.

The 150 scientists who gathered at the Asilomar Conference Grounds under the auspices of the National Academy of Sciences represented 16 countries. Among them were virtually all the leaders in this new field of microbial genetics.

And although their laboratories compete as bitterly as baseball teams for first place in the discovery race, they reached near-unanimous agreement on their general guidelines for public safety in their future experiments.

To these scientists, Dr. Sidney Brenner, a distinguished British biologist from Cambridge, declared

"We have created a new set of principles here. But it is your individual judgment and your individual behavior which will determine what you do.

"We ourselves have no power other than the moral suasion we can exercise among our colleagues."

To this thought Dr. A. A Bayev, of the Institute of Molecular Biology in Moscow, declared that Soviet scientists "fully realize the biohazards" in experiments with genetically-hybrid organisms, and accept the obligation to act with "prudence for the safety of our laboratory workers, mankind and the environment."

The long and complex draft of the conference recommendations will now be formalized in greater detail by Berg and his colleagues for official approval by American's National Academy of Sciences.

Beginning today in San Francisco, a special advisory committee of the National Institutes of Health will undertake the difficult job of drafting detailed safety standards that will officially regulate the experiments of American scientists working in this new frontier field of biology.

# Genetic manipulation: guidelines issued

The NIH ground rules for genetic manipulation experiments may not mark the end of an unprecedented debate within the scientific community. **Colin Norman** reports from Washington

AFTER two years of controversy and uncertainty, the National Institutes of Health (NIH) last week issued a complex set of guidelines governing the use of a powerful new technique for manipulating genes in living organisms. The guidelines establish safety rules for experiments which may revolutionize biology, but which also provide man with unprecedented ability to alter the characteristics of living things. They are, however, far from being the final word on whether, and under what circumstances, such research should be allowed to go ahead, for they are already being overtaken by events in some places.

On July 7, for example, the City Council in Cambridge, Mass., will vote on a resolution, proposed by the Mayor, which would ban for two years all such experiments at Harvard and MIT. And months of bitter debate at the University of Michigan have resulted in the adoption of regulations there which are more strict than those issued by NIH last week. The focus of the debate is clearly shifting from Washington into the university communities where the research will take place.

Nevertheless, the NIH guidelines will provide important ground rules for genetic manipulation experiments in many institutions, and their impact will extend far beyond the borders of the United States, for they are likely to influence the establishment of guidelines in many other countries. They have been developed by an extraordinary process of self-regulation by the scientific community.

The process began in 1973, when scientists familiar with the nascent technique began to worry about potential hazards associated with its use. Their concerns led a committee of the National Academy of Sciences to issue a public statement in July 1974, urging scientists around the world to defer two types of experiments until the hazards have been defined. The moratorium lasted until last February, when it was partly replaced by general guidelines recommended by an international group of geneticists which met at Asilomar, California. Then an NIH advisory committee, consisting of scientists, took centre stage. It laboured hard during most of last year trying to cast the Asilomar guidelines into more specific rules, completing its task by hammering out a set of complex proposals last December. The proposals went to NIH Director Donald S. Fredrickson, who called a public meeting to discuss them, solicited the views of numerous scientists and non-scientists, and asked the advisory committee to reconsider some of its suggestions. The guidelines issued last week represent Fredrickson's distillation of the conflicting advice presented to him.

They differ a little in detail, but not in philosophy, from the recommendations of the advisory committee. They will allow most planned experiments to go ahead, albeit under strict safety controls, outlawing only a handful of the more hazardous types of experiments. They are, however, stricter than the Asilomar guidelines, a fact which Fredrickson suggested means that "the research will go forward in a manner responsive and appropriate to hazards that may be realised in the future". And Dr DeWitt Stetten, Deputy NIH Director for Science and chairman of the advisory committee, argued last week that "the issuance of the guidelines is in no sense an opening of the floodgates, rather it is a closing of the leaks (in the Asilomar guidelines)".

Be that as it may, the guidelines are not even NIH's final say on the matter. Their publication falls under the terms of the National Environmental Policy Act, which means that NIH must prepare an assessment of the potential impact of the research on the environment. A draft assessment should be ready by September, and since it will be opened up for public comments before being cast in final form, another round of discussion of the risks and benefits of the research is in store. In the meantime, the guidelines will take effect, governing NIH's support of the research.

### New dimension

Why have the guidelines taken so long to produce, and caused so much strife? The answer is that the research offers a spectacular mix of potential benefits and possible hazards, and it opens up an entirely new dimension in biology. The experiments consist, in short, of snipping genes from the DNA of any organism and splicing them into the DNA of another, perhaps entirely unrelated, organism. The resulting molecule—a recombinant DNA molecule—is copied (cloned) each time the new host reproduces, producing large quantities of the transplanted genes. The technique offers a powerful tool for probing the working of genes and their arrangement in complex organisms and, more distantly, it may offer a means of constructing special micro-organisms for a variety of medical, commercial and industrial uses.

But the worry is that the technique allows biologists to breach genetic barriers between species which have evolved over thousands of years. In short, it allows biologists to by-pass the processes of evolution. More specifically, foreign genes inserted into an organism may cause that organism to behave in a dangerous, and perhaps unpredictable, manner. The guidelines thus seek to ensure that micro-organisms bearing transplanted genes are contained in the laboratory.

They spell out our levels of physical containment to be used in such experiments, designated P1 to P4, ranging from use of standard microbiological techniques (P1) to the use of specially equipped facilities akin to biological warfare laboratories (P4). And, as a second line of defence, they spell out three levels of biological containment, EK1 to EK3, which must be used for experiments involving the insertion of genes into a strain of the common gut bacterium *E. coli*—the organism which will be used for most experiments. The levels are as follows:

- EK1—use of standard *E. coli* K12, a laboratory strain of *E. coli* which has been used for genetic experiments for decades. Foreign genes are inserted into the bacterium by splicing them into a plasmid (a ring of bacterial DNA which reproduces independently from the bacterium's chromosomes) and reintroducing the recombinant into the bacterium, or by splicing them into the DNA of a bacteriophage which then infects *E. coli* K12.

- EK2—the use of specially mutated strains of *E. coli* or bacteriophage which, according to laboratory tests, are virtually incapable of surviving outside the laboratory so that the recombinant DNA will have less than 1 in $10^{-8}$ chances of surviving in the natural environment.

- EK3—the same as EK2 except that the survivability has been tested in animals, plants and other environments.

The guidelines assign specific physical and biological safety levels to various types of experiments on the basis of their potential hazards (see box). They

also spell out safety rules for experiments involving recombinants formed by splicing genes into the DNA of animal viruses, which are then grown in cell cultures to provide multiple copies of the foreign genes. The final guidelines alter some of the containment levels proposed by the advisory committee, but no substantial alterations have been made.

**Cautious approach**

How did Fredrickson arrive at his final decision when confronted with such a wealth of conflicting advice? His first, and most fundamental, consideration was simply whether the research should be allowed to go ahead at all, in view of the potential hazards. The majority of the commentators on the guidelines recommended that it should, but he was advised to take an extremely cautious approach by two of the most eminent of the commentators, neither of whom intends to conduct experiments with recombinant DNA.

Dr Robert Sinsheimer, chairman of the Department of Biology at California Institute of Technology, argued in a letter to Fredrickson that the experiments present a serious hazard if they breach the genetic barrier between higher organisms (eukaryotes) and lower organisms (prokaryotes). "One need not continue to spin out potential horror stories", he wrote, "the point is that we will be perturbing, in a major way, an extremely intricate ecological interaction which we understand only dimly". As for the guidelines themselves, Sinsheimer stated: "I cannot believe that under these proposed guidelines the organism can be contained. If the work is going on in a hundred laboratories about the United States, performed by technicians, graduate students, etc., the organism will inevitably escape—and will enter into the various ecological niches known to be inhabited by *E. coli*." He therefore proposed that all work with recombinant DNA should be performed under maximum containment conditions at a single institution in the United States, and that there should be an intensive effort to seek a microorganism more suitable than *E. coli* for the work.

The other eminent, though more flamboyant, critic of the guidelines, Erwin Chargaff of Columbia University, recommended that all work on recombinant DNA should be halted for at least two years to allow time for the hazards to be assessed. Chargaff asked, in a letter published in *Science*, "Have we the right to counteract, irreversibly, the evolutionary wisdom of millions of years, in order to satisfy the ambition and the curiosity of a few scientists?"

The advisory committee did not consider Sinsheimer's or Chargaff's pro-

# Guidelines in detail

The guidelines define four levels of physical containment, designated, in order of increasing stringency, P1 to P4, and three levels of biological containment, EK1 to EK3, and assign experiments to them on the basis of potential risk. The following is a summary of containment levels specified for various sources of DNA.

**a.** Shotgun experiments using *E. coli* as the host

| | |
|---|---|
| Non-embryonic primate tissue | P3+EK3 or P4+EK2 |
| Embryonic primate tissue or germ line cells | P3+EK2 |
| Other mammals | P3+EK2 |
| Birds | P3+EK2 |
| Cold blooded vertebrates, non-embryonic | P2+EK2 |
| embryonic or germ line | P2+EK1 |
| If vertebrate produces a toxin | P3+EK2 |
| Other cold blooded animals and lower eukaryotes | P2+EK1 |
| If Class 2 pathogen*, produces a toxin, or carries a pathogen | P3+EK2 |
| Plants | P2+EK1 |
| Prokaryotes that exchange genes with *E. coli* | |
| Class 1 agents (non-pathogens) | P1+EK1 |
| Low risk pathogens (for example, enterobacteria) | P2+EK1 |
| Moderate risk pathogens (for example, *S. typhi*) | P2+EK2 |
| Higher risk pathogens | banned |
| Prokaryotes that do not exchange genes with *E. coli* | |
| Class 1 agents | P2+EK2 or P3+EK1 |
| Class 2 agents (moderate risk pathogens) | P3+EK2 |
| Higher pathogens | banned |

In all above cases, if DNA is at least 99% pure before cloning and contains no harmful genes, either physical or biological containment levels can be reduced one step.

**b.** Cloning plasmid, bacteriophage and other virus genes in *E. coli*

| | |
|---|---|
| Animal viruses | P4+EK2 or P3+EK3 |
| If clones free from harmful regions | P3+EK2 |
| Plant viruses | P3+EK1 or P2+EK2 |
| 99% pure organelle DNA, Primates | P3+EK1 or P2+EK2 |
| other eukaryotes | P2+EK1 |
| Impure organelle DNA: shotgun conditions apply. | |
| Plasmid or phage DNA from hosts that exchange genes with *E. coli* | |
| If plasmid or phage genome does not contain harmful genes or if DNA segment 99% pure and characterised | P1+EK1 |
| Otherwise, shotgun conditions apply. | |
| Plasmids and phage from hosts which do not exchange genes with *E. coli* | |
| Shotgun conditions apply, unless minimal risk that recombinant will increase pathogenicity or ecological potential of the host, then | P2+EK2 or P3+EK1 |

NB. cDNAs synthesised *in vitro* from cellular or viral RNAs are included in above categories.

**c.** Animal virus vectors

| | |
|---|---|
| Defective polyoma virus+DNA from non-pathogen | P3 |
| Defective polyoma virus+DNA from Class 2 agent | P4 |
| If cloned recombinant contains no harmful genes and host range of polyoma unaltered, reduce to | P3 |
| Defective SV40+DNA from non-pathogens | P4 |
| If inserted DNA is 99% pure segment of prokaryotic DNA lacking toxigenic genes, or a segment of eukaryotic DNA whose function has been established and which has previously been cloned in a prokaryotic host-vector system, and if infectivity of SV40 in human cells unaltered | P3 |
| Defective SV40 lacking substantial section of the late region+DNA from non-pathogens, if no helper used and no virus particles produced | P3 |
| Defective SV40+DNA from non-pathogen can be used to transform established lines of non-permissive cells under P3 provided no infectious particles produced. Rescue of SV40 from such cells requires | P4 |

**d.** Plant host-vector systems

P2 conditions can be approximated by insect-free greenhouses, sterilization of plant, pots, soil and runoff water, and use of standard microbiological practice.

P3 conditions require use of growth chambers under negative pressure and routine fumigation for insect control.

Otherwise, similar conditions to those prescribed for animal systems apply.

*Classes for pathogenic agents as defined by the Center for Disease Control.

posals during its public meetings, but Fredrickson alluded to them in a lengthy statement published along with the guidelines. Recognising that the breaching of genetic barriers might pose a hazard, Fredrickson nevertheless argued that the research can be controlled so that it is carried out safely. Noting that "the international scientific community . . . has indicated a desire to proceed with research in a conservative manner", and that "most of the considerable public commentary on the subject, while urging caution, has also favoured proceeding", Fredrickson pointed out that there is, in any case, no way to prohibit the research throughout the world. "There is," he added, "no reason to attempt it."

Having decided that there should be no flat proscription on the research, Fredrickson turned to some of the chief concerns raised by the critics of the guidelines. The most prominent concern arises from the fact that most work with recombinant DNA will take place with the *E. coli* K12 bacterium. Since *E. coli* is a common inhabitant of the human gut, many observers have considered it a dangerous choice for the research. In particular, a group of scientists from the Boston area urged that a different host for transplanted genes be developed, and that the use of *E. coli* be phased out as swiftly as possible.

Fredrickson argues, however, that since the bacterium has been used for decades as the geneticists' workhorse, there is extensive knowledge of its behaviour and, moreover, there is good evidence that it is unlikely to survive for long in the environment in competition with wild strains of *E. coli*. In other words, *E. coli* K12 itself provides a level of biological containment. "I believe that because of this experience, *E. coli* K12 will provide a host-vector system that is safer than other systems", Fredrickson argued, and he declined to set a limit on when it should be phased out of the research.

Another area of concern with the proposed guidelines centred on how they should be implemented, and that section has been extensively revised. The guidelines strictly apply only to research supported by NIH, and investigators must comply with them before they can receive a grant. Some commentators suggested that principal investigators be required to obtain informed consent from all laboratory personnel before proceeding with recombinant DNA experiments, but Fredrickson opted instead for a requirement that the investigators simply inform all laboratory workers of the real and potential hazards associated with the experiments.

The guidelines also require that each institution where recombinant DNA experiments will be conducted should establish a biohazards committee, to ensure that facilities meet specified requirements, training is adequate and so on. The advisory committee had firmly recommended that such committees should not be responsible for determining the containment conditions for specific experiments, but Fredrickson deleted that prohibition, leaving the matter up to individual institutions.

A final point concerning implementation which is clearly worrying many people is that the guidelines do not apply to industry. Early last month, however, Fredrickson briefed officials from various industries on the guidelines and received from them expressions of support for their intent and their general provisions. Some officials expressed reservations about specific items, however, such as the provision prohibiting large-scale experiments with recombinant DNA, and the Pharmaceutical Manufacturers' Association has decided to convene a committee to review whether the guidelines are applicable to the drug industry.

**Effect of guidelines**

Now that these guidelines have been issued, how do they affect academic scientists conducting, or hoping to conduct, recombinant DNA experiments? First, they specify that many experiments should use EK2 or EK3 biological containment, and until crippled micro-organisms which meet those criteria are available, such experiments should not be conducted. The advisory committee which drafted the guidelines is responsible for certifying whether crippled strains meet the criteria.

A strain of *E. coli* produced by Roy Curtiss of the University of Alabama (called $\psi$1776) has been proposed as an EK2 system with two specific plasmids (pSC101 and Col EI-*kan*). Curtiss, who has built many crippling mutations into the bacteria in an effort which took the best part of a year, has provided the committee with reams of data on its survivability. Last month, a subcommittee voted unanimously that the strain meets the EK2 specifications, and the full committee is expected to approve it in the next few weeks. That would pave the way for many experiments.

But a confusing situation has developed with respect to two other candidate EK2 strains. At its last meeting in April, the committee approved a strain of bacteriophage lambda, developed by Philip Leder of NIH as an EK2 strain. But a subcommittee which met last month to consider a second candidate strain, developed by Fred Blattner at the University of Wisconsin, was divided on a matter which affects both strains. In short, two subcommittee members refused to endorse the use of either phage as an EK2 system unless they are used in conjunction with crippled bacteria. The full committee will take up that thorny issue when it next meets in September. Curtiss's *E. coli* strain, incidentally, is resistant to infection by phage $\lambda$.

Many of the objections and reservations which critics have levelled at the guidelines are now beginning to crop up in local debates in and around the universities where the research will be conducted. In that regard, the situation brewing in Cambridge, Mass., may be an indication of things to come. It began quietly a few months ago, when some researchers at Harvard proposed that a laboratory, meeting P3 requirements, be established in the Harvard Biology Labs. The facility, which would cost some $350,000, would have involved converting some existing laboratory space, and the intent was to undertake a variety of work in it, including some recombinant DNA experiments.

The proposal met with opposition within Harvard, however, largely because the biology labs are old, infested with cockroaches and with a species of ant which has so far evaded attempts at eradication. In short, critics suggested that the building is unsuitable for a P3 facility. Their criticisms broadened into an assault on the proposal to conduct recombinant DNA experiments at Harvard, however, and the dispute spilled over into the city when the matter was reported at length in Boston's weekly newspaper.

Approval of the laboratory by the Harvard authorities was all but assured, since the concept had been endorsed by a biohazards committee, Harvard's Committee on Research Policy, and the Dean of Arts and Sciences. But, when he read about the dispute in the newspapers, Cambridge city Mayor Alfred Velucci stepped in. He called a council meeting on June 23—ironically the day the NIH guidelines were issued—to discuss the matter, and a string of scientists testified about the potential hazards and benefits of recombinant DNA research. By all accounts, the atmosphere was highly charged, and there was considerable heated discussion.

The matter has now gone well beyond the issue of whether the laboratory should be built, however, for Velucci has introduced a resolution which would prohibit all recombinant DNA experiments in Cambridge—even those deemed to have minimal risk—for two years. The council will vote on the resolution on July 7, and the outcome will be closely watched around the country. □

APPENDIX E

UCSF News Services

y of California San Francisco 1475 Fourth Avenue San Francisco,California 94143 Telephone:(415) 666-25

Michela Reichman, Campus Director
News Services and Publications

FOR IMMEDIATE RELEASE

For more information contact
Michela Reichman, 666-2557

SAN FRANCISCO, Oct. 5 -- A new biosafety committee has been created at the University of California San Francisco to inventory, monitor and maintain safeguards for research in genetic engineering, known as recombinant DNA, it was announced today by Francis A. Sooy, M.D., Chancellor. The 13-member committee includes two public members in addition to UCSF researchers and a professor of bioethics, Chancellor Sooy declared.

Chairman of the Committee is David Martin, Jr., associate professor of medicine, biochemistry, and biophysics, who is not involved in DNA research himself. Only three scientists on the committee are doing the DNA work: Boyer, Goodman and McCarthy.

Members of the committee include:

| | |
|---|---|
| Herbert Boyer, Ph.D. | Biochemistry |
| James Cleaver, Pn.D. | Radiobiology |
| Louis Diamond, M.D. | Pediatrics/Cancer Research Institute |
| Howard Goodman, Ph.D | Biochemistry/Biophysics |
| Christine Guthrie, Ph.D. | Biochemistry/Biopnysics |
| Keith Hadley, Ph.D. | Laboratory Medicine/Microbiology |
| Albert Jonsen, Ph.D. | Bioethics/Health Policy Program |
| David Martin, Jr., M.D., Chairman | Medicine/Biochemistry/Biophysics |
| Brian McCarthy, Ph.D. | Biochemistry/Biophysics |
| Harold Varmus, Ph.D. | Microbiology |
| Francis Curry, M.D. | Public Health (Former Director) |
| Thomas W. Mellon | Public Member (Outgoing CAO for S.F.) |
| (To be Appointed) | Public Member |

The charge of the committee, which functions through the Academic Senate office, according to Chancellor Sooy, is to conform to regulations issued by the U.S. Department of Health, Education and Welfare in connection with any research dealing with genetic engineering, in order to protect both the public and laboratory workers against any possible contamination. The specific charge is to:

1) Advise the institution on policies.

2) Create and maintain a central reference file and library of catalogs, books, articles, newsletters and other communications as a source of advice and reference regarding, for example, the availability and quality of the safety equipment, the availability and level of biological containment for various host-vector systems, suitable training of personnel, and data on certain recombinant DNA's.

3) Develop a safety and operations manual for facilities maintained by the institution and used in support of recombinant DNA research.

4) Certify to the NIH on applications for research support and annually thereafter, that facilities, procedures and practices and the training and expertise of the personnel involved have been reviewed and approved by the institutional Biosafety Committee.

# # #

# A letter from the Chancellor: Recombinant DNA

March 16, 1977

TO: Members of the campus community and friends of UC-San Francisco

☐ My original intention in starting this newsletter was not simply to keep you abreast of developments in our building program, but to take the opportunity from time to time to go into broad issues of mutual concern and interest in the areas of education and training of health professionals, patient care and community outreach, research and the delivery of health care — as they affect this campus, the city, the state and the nation. I would like to spend some time therefore to discuss in depth what is happening today in modern biology.

☐ **The speed of new knowledge in the biomedical sciences is astounding. With all modesty I must point out that because of work done on our campus,** tiny babies all over the world are being saved who before would never have achieved a normal life; thousands of persons born deaf may soon hear almost normal speech; people with tumors the size of a pin-head on their pituitary glands are being operated on successfully without damage to their brain; a fundamental mechanism in the development of certain skin cancers is now known; and bacteria that convert sunlight into energy have been discovered.

But it must be pointed out that the search for knowledge and for control of our world has been a continual struggle with the unknown and with our own fears and ignorance. Each new discovery necessarily has led us into unknown situations and exposed us to new risks and dangers. Madame Curie died of X-rays she gave the world; our own Karl Meyer was criticized for working with psittacosis because it was so dangerous, but it is because of his work that people are not dying of it today.

It is in this context that I would like to discuss with you some of the issues in the current public discussions about the exciting new research tool in genetics called "recombinant DNA" by the scientists and "gene splicing" or "genetic engineering" in the press. It is appropriate, for scientists on this campus have been in the forefront in developing the technique that has made this possible, as well as in developing maximum safety guidelines and regulations, just as our campus took leadership some years ago in developing guidelines for Committees on Human Research, which now have become routine procedure for research institutions in this country.

What is "DNA"? It stands for the initials of the chemical substance which forms the long, alphabet-like blueprint for building, duplicating, operating and repairing the genes of cells in nearly every living thing. It is a particular segment of DNA which defines, for example, whether a cell will become a muscle or an eye.

☐ **Some five years ago, scientists at UCSF and Stanford developed a simple technique which made it possible to split apart and then splice together DNA from different genes** (or segments of genes) in bacteria, and thereby "recombine" them. In so doing, they were duplicating in the test tube the process of genetic exchange which nature has been carrying out in bacteria (and all higher organisms — including humans) since the beginning of life . . . In short, what bacteria do to themselves by the billions daily.

However, the scientists at that time were troubled enough by the possible hypothetical hazards (still not identified) to impose a temporary moratorium on their own activities while they studied the situation. The dangers from improper laboratory safety measures were a concern.

In February, 1975, leading geneticists, molecular biologists, biochemists and others from all over the world met at Asilomar to iron out safety guidelines. Some reporters were invited, and the meeting was published widely in the lay press. These voluntary guidelines were extended through the National Institutes of Health and made mandatory for all recipients of NIH grants. However, they did not apply to laboratories not funded by NIH, nor did they apply to industrial or commercial laboratories. There was considerable controversy in the scientific press over whether or not these guidelines were adequate. The official NIH guidelines finally were issued by the Director in July, 1976. While not yet law, they carry enormous weight, since most scientists are dependent upon NIH funding to carry out their research.

☐ **Under the National Institutes of Health guidelines, experiments in genetic manipulation in living organisms call for facilities with varying degrees of physical containment capability,** ranging from "P-1" to "P-4", according to the degree of potential hazard involved.

On our UCSF campus there are several "P-1" laboratories, one "P-2" laboratory and one "P-3" laboratory, which is where our recombinant DNA work is carried out. The latter is limited at present to use by the five investigators and their properly trained staffs, and conducted under the most rigorous interpretation of the NIH guidelines.

The guidelines also set a series of biological levels of control which are by far the most effective. They allow only those strains of bacteria to be used which cannot survive outside the test-tube. They also classify all artificial recombinant DNA experiments on the basis of potential hazard, and forbid the use of any dealing with dangerous human pathogens or unauthorized release of artificial organisms into the biosphere; and, finally, they require the establishment of broadly based committees on all campuses, containing both scientists and non-scientists, charged with certification and monitoring of all this work, as well as exchanging information on and off campus.

☐ **Last year UCSF established a Biosafety Committee with the responsibility of ensuring strict adherence to guidelines established by the National Institutes of Health** for all work they fund in recombinant DNA. Indeed, the committee has gone farther than the NIH regulations, and also has assumed the same responsibility for work done in other areas of biological research.

It consists of UCSF scientists and one technician plus several public members, including Thomas J. Mellon, the former Chief Administrative Officer for the city of San Francisco, Francis J. Curry, M.D., the former Director of Public Health for San Francisco (who now is a member of the faculty of UCSF), and Lucy McCabe, an attorney who has been active with the California Rural Legal Assistance. The campus officer for Health and Environmental Safety is an ex officio member. Chairman is David W. Martin, Jr., M.D., a medical geneticist and biochemist not involved in recombinant DNA work, and Vice-Chairman is Albert R. Jonsen, Ph.D., Associate Professor of Bioethics at UCSF, who is a national leader in public policy discussions on many aspects of medical and scientific bioethics.

☐ **The UCSF Biosafety Committee has made a strong effort to do its work in the public spotlight and to educate the public, other institutions and the campus community about safety precautions.**

Public announcements were made at the time of the formation of this committee; its meetings and minutes are open to the public. It is now in the process of making an inventory of all biological research on campus (not just recombinant DNA technology) for which safety guidelines are applicable.

Many of our people are acting as resource to individuals and legislative bodies attempting to develop constructive regulations which will meet the problems raised without destroying the ability to perform this important research. Both Herbert Boyer and Professor Jonsen testified in

Sacramento before the Keene hearings; Dr. Boyer participated in the recent National Academy of Sciences seminar in Washington, D.C.; and Dean Julius R. Krevans of our School of Medicine served on a national committee created by NIH to review its guidelines and make recommendations for improvement and implementation. Dr. Boyer was one of the original group of scientists responsible for the Asilomar conference.

In addition to the public members on our Biosafety committee, I personally have informed Mayor Moscone, Chief Administrative Officer Boas, President Kopp of the Board of Supervisors and Acting Health Director Dr. Smookler of our activities.

- **UCSF and Stanford scientists who first developed the recombinant DNA technology** proposed to their respective institutions and NIH that a patent be applied for — primarily to ensure that the same regulations would be enforced by industry and private firms engaged in commercial exploitation of this knowledge.

- **In July,1976, the Cambridge City Council held heated and highly publicized public hearings** about work proposed at Harvard and MIT, after which it instituted a temporary moratorium on these experiments while a panel of scientists and lay persons studied the situation. After much study, the City Council advised Harvard to go ahead with recombinant DNA work, and Harvard is proceeding with the construction of a new building for such a facility, under regulations set by the city as well as NIH.

  Other cities and at least two other states have been studying DNA research activity in their areas. Both Sen. Kennedy and Sen. Dale Bumpers will have national regulatory legislation before Congress this session. The city of San Diego looked closely at UC-San Diego's projects and now has agreed that that institution may go ahead. Berkeley City Council is beginning to study its situation, primarily with regard to private and commercial development, and UC-Berkeley has offered to help the city in this. The legislation proposed by State Assemblyman Keene after his joint committee hearings calls for regulation of commercial as well as academic laboratories engaged in this work.

  Specifically, it calls for the establishment of a 17-person commission to establish temporary guidelines by February, 1978 and permanent guidelines by March, 1978 for "all hazardous biological research in the state," and would require all researchers to apply to the commission for certification of research in which they are involved — industrial and commercial as well as academic. The guidelines would have to be "no less stringent" than those of the NIH.

- **A number of questions have been raised about research in recombinant DNA, and scientists have testified and written on both sides of these issues.** Safety is a prime concern. Another concern is the need to apply the same guidelines to regulation of commercial exploitation of this knowledge as is applied now to NIH-funded academic laboratories.

  Other concerns expressed range from the ethics of tampering with the genetic pool, to the possible results if such information were placed in the wrong hands. Some people are calling for a ban on all research done with recombinant DNA technology because of what "might happen" in the future.

  I should emphasize that, unlike some of the other scientific research done all over the world, most of the "dangers" in recombinant DNA work are hypothetical, as Prof. Jonsen points out below. The safety precautions, on the other hand, which are covered by the NIH guidelines, are parallel to similar regulations initiated in previous years when similar concerns were identified about work in radioactive materials, viruses and other biomedical research and therapy.

  It cannot be denied that the intense concern about recombinant DNA research, shown by some scientists and some members of the public, reflects in part a suspicion of science and technology which is a spin-off from what is seen as improper use in prior times of the results of developments in nuclear physics and chemical and bacteriological warfare. In connection with this it should be pointed out that it was the *Scientists* who warned the public of the dangers in both these areas.

Sculptures depicting the initial meeting of Swanson and Boyer in late 1975. With the living originals.

UCSF NEWS SERVICES / PUBLICATIONS

versity of California San Francisco 1475 Fourth Avenue San Francisco,California 94143 Telephone:(415) 666-2557

Michela Reichman, Campus Director
News Services and Publications

For further information call
666-2557

FOR IMMEDIATE RELEASE
September 26, 1977

University of California San Francisco spokesmen declared today that the premature use of a plasmid vector in recombinant DNA experiments before the plasmid was certified by the National Institutes of Health was in no way hazardous, and the NIH since then has certified the plasmid (pBR322) as being entirely safe for this research.

According to William O. Reinhardt, M.D., Acting Dean of the School of Medicine, the plasmid was used for a short time early this year in the UCSF P3 laboratory in experimentation with the rat insulin gene.

The UCSF Biosafety Committee is continuing to investigate this incident and is taking steps to prevent such an episode from happening again, Dean Reinhardt declared.

"The premature use early this year of pBR322," Dean Reinhardt declared, "was due to the fact that the researchers understood that it had been approved for use by the NIH Recombinant DNA Committee.

" When the investigators learned a few weeks late that the plasmid had not in fact been certified, they stopped the cloning experiments with pBR322. Subsequently," Dean Reinhardt declared, "the experiments were carried out with a plasmid (pMB9) that was certified, and the results were communicated in an article in Science Magazine of June 17, 1977." (A full statement is attached.)

Under the NIH guidelines for this research, popularly called "gene splicing", a national NIH committee must give approval, followed by written certification, of

Plasmid vector 2-2-2-2

any plasmid vector before it can be used. Plasmids are small circular bits of DNA (the material containing genetic information), which can reproduce themselves within host bacteria. Bits of DNA containing genes from plants, animals or other bacteria can be spliced onto these plasmids. The foreign genes are then reproduced, along with the plasmids, in a process called "cloning".

The announcement in June of the cloning of the rat insulin gene by the UCSF team received world attention, for it opened the possibility of eventually being able to mass produce human insulin, Dean Reinhardt declared, and has made possible developments with the potential for much social good.

The incident is described in an article published in Science Magazine this week.

UCSF University of California San Francisco
NEWS SERVICES / PUBLICATIONS
1475 Fourth Avenue San Francisco,CA 94143 (415) 666-

FILE COPY

Michela Reichman, Campus Director
News Services and Publications

FOR YOUR INFORMATION

NOT FOR RELEASE UNTIL FRIDAY, A.M.
DECEMBER 2, 1977

For further information contact:
Sydney J. Keith or Saul W. Abel,
City of Hope, (213) 626-4611;
Joel Gurin, UC-San Francisco, (415) 666-2557

Memo to: Science Writers, Assignment Editors
Subject: This announcement will be made by City of Hope at a press conference they have scheduled for Thursday, December 1, 1977 at 1:00 p.m. in the Cordovan Room of the Biltmore Hotel, downtown Los Angeles.
The press conference is being co-ordinated by Sydney Keith and Saul Abel of the City of Hope; they can be reached at the above number or at the Biltmore, (213) 624-1011, on the day of the conference.
Those who cannot attend this press conference, but who would like to interview Dr. Boyer in San Francisco before, should contact Joel Gurin at UCSF. We will be happy to arrange this for you.

A team of scientists working at the City of Hope, Los Angeles, and at UC-San Francisco say that their successful production of the hormone, somatostatin, in bacteria demonstrates that bacteria can be used safely as "factories" to produce much needed medically useful biological materials.

The researchers used recombinant DNA techniques to introduce an artificial gene into bacteria, which were "commanded" by the gene to produce the mammalian hormone somatostatin--the first time that a medically useful hormone has been produced in bacteria. The genetic engineering feat, reported in the December 9 issue of Science, has been described as "a scientific triumph of the first order" by Philip Handler, President of the National Academy of Sciences.

Especially significant are the special safety features incorporated into this experiment, which the investigators will describe at the press conference. According to the researchers, virtually identical techniques could be used safely in bacteria to produce complex biological substances ranging from insulin and other hormones to the enzymes used in industrial fermentation.

Present at the press conference will be the three principal authors of the paper:

Keiichi Itakura, Ph.D., City of Hope;
Arthur D. Riggs, Ph.D., City of Hope;
Herbert W. Boyer, Ph.D., UC-San Francisco.

Rachmiel Levine, M.D., Executive Medical Director of the City of Hope National Medical Center and a diabetologist, will be present to discuss possible clinical implications of the somatostatin experiment.

11/23/77

#

UCSF University of California San Francisco
NEWS SERVICES / PUBLICATIO
1475 Fourth Avenue San Francisco,CA 94143 (415)

ela Reichman, Campus Director
ws Services and Publications

NOT FOR RELEASE UNTIL FRIDAY, A.M.,
DECEMBER 2, 1977

For further information contact:
dney J. Keith or Saul W. Abel,
City of Hope, (213) 626-4611;
Joel Gurin, UC-San Francisco, (415) 666-2557

Released Jointly by City of Hope National Medical Center, Los Angeles and the University of California San Francisco in connection with publication in Science Magazine of December 9, 1977.

A team of scientists working at the City of Hope, near Los Angeles, and at UC-San Francisco said today that their successful production of the hormone somatostatin in bacteria demonstrates that bacteria can be used safely as "factories" to produce much needed medically useful biological materials.

The genetic engineering feat, reported in the current issue of the magazine Science (December 9, 1977), was described as "a scientific triumph of the first order" by Philip Handler, President of the National Academy of Sciences in testimony before the Senate Subcommittee on Commerce hearings on research with Recombinant DNA on November 2.

Keiichi Itakura, Ph.D., and Arthur D. Riggs, Ph.D. of the City of Hope, and Herbert W. Boyer, Ph.D. of UCSF, were spokesmen for the group, which includes Tadaaki Hirose and Roberto Crea of the City of Hope, and Herbert L. Heyneker and Francisco Bolivar of UCSF, all Ph.D.'s.

The researchers used recombinant DNA techniques to introduce an artificial gene into bacteria, which were "commanded" by the gene to produce the mammalian hormone somatostatin. Since the experiment included special safety features, the scientists said that it not only represents "the first demonstrated practical benefit from recombinant DNA technology," but also shows that such benefits can be achieved safely.

The reason that the technique developed by the City of Hope-UCSF team is so safe, they said, is because bacteria are made to produce an inactive precursor of the hormone. Once the protein is extracted from the cell (a process whcih kills the bacteria), it is transformed, using a simple chemical procedure, into the active form, which is somatostatin.

to the bloodstream, it is a valuable tool for the study of hormone action -- and it may prove useful in the treatment of diabetes, acute pancreatitis (inflammation of the pancreas), and the hormone disorder acromegaly.

According to City of Hope and UCSF researchers, other scarce but important hormones -- such as insulin and growth hormone -- now theoretically could be produced with recombinant DNA techniques, perhaps in quantities previously unavailable. Experimental and clinical work with growth hormone has been slowed by the difficulty of obtaining it from natural sources; if it were more readily available, the researchers said, growth hormone might be used to treat cases of pituitary dysfunction.

The work with somatostatin represents the coming together of two of the newest fields in biochemical research: artificial gene synthesis and the use of recombinant DNA techniques.

Six years ago Har Gobind Khorana of the Massachusetts Institute of Technology synthesized the first artificial gene. It contained genetic information that normally makes a certain kind of RNA in yeast. An alternate method of chemical synthesis -- the method used in the somatostatin experiment -- was developed by Itakura and his colleagues at the City of Hope.

Recombinant DNA techniques -- which provide the technology for transplanting artificial and natural genes from any species into bacteria -- have been developed since 1973. Stanford's Paul Berg and Stanley Cohen, and Boyer at UCSF, are credited with originating the methods of recombinant DNA research. Boyer is an investigator of the Howard Hughes Medical Research Institute.

The somatostatin work at both City of Hope and UCSF was funded by contracts from Genentech, Inc.

---

Details of the somatostatin experimental procedure are given below.

Recombinant DNA technology provides methods of using enzymes to join DNA from different species. (DNA is the double-spiral, threadlike substance of heredity, and genes are sections of DNA.) With the new techniques, scientists now can "snip" DNA apart and "sew" it together with the precision of a master tailor.

(more)

The first step in the City of Hope-UCSF experiment was the chemical thesis of a gene for somatostatin. Since they knew the fourteen amino acids hat make up the hormone and the order in which they are linked together, the researchers were able to synthesize a piece of DNA containing the correct genetic code. Elements were added to provide restriction sites, where enzymes acted to produce biochemically "sticky" ends that facilitated later reassembly.

Next, the scientists [illegible] to insert their gene into a plasmid vector -- the circular ring of bacterial DNA that would carry the gene inside E.Coli bacteria. They used a modified form of the plasmid pBR322, into which a natural gene called the lac operator had been spliced with enzymes. In nature, the lac operator is a genetic switch that turns on and turns off the genes that make a certain enzyme in bacteria. The researchers hoped that they could turn on the gene for somatostatin -- and cause the bacteria to make the hormone -- by putting the artificial gene next to the lac operator in the plasmid.

The design for the experiment included built in safeguards that virtually eliminated any risks of dangerous effects. The synthesized gene was deliberately formulated to produce a large precursor molecule -- a hybrid of somatostatin and a bacterial enzyme -- which is inactive until treated with the chemical cyanogen bromide.

This hybrid yielded pure synthetic somatostatin after chemical treatment. Several tests showed that this synthetic hormone had the same chemical properties and biological activity as natural somatostatin isolated from animals. The researchers concluded t[illegible] they had achieved "the first expression of a peptide product from a gene of chemically synthesized origin."

The work with somatostatin was carried out in a P3 containment laboratory according to guidelines established by the National Institutes of Health.

#

Scanner Ready -- Courier

REGIS McKENNA PUBLIC RELATIONS
348 Waverley Street
Palo Alto, California 94301
Regis McKenna (415) 329-0810

For:

GENENTECH, INC.
460 Point San Bruno Boulevard
So. San Francisco, California 94080
Robert Swanson (415) 952-0123

FOR RELEASE 12 NOON
SEPTEMBER 6, 1978

# FIRST SUCCESSFUL LABORATORY PRODUCTION OF HUMAN INSULIN ANNOUNCED

SO. SAN FRANCISCO, CA, September 6, 1978--Genentech, Inc. and City of Hope National Medical Center, a private research institution and hospital in Duarte, California today announced the successful laboratory production of human insulin using recombinant DNA technology.

Insulin is a protein hormone produced in the pancreas and used in the metabolism of sugar and other carbohydrates. The synthesis of human insulin was done using a process similar to the fermentation process used to make antibiotics. The achievement may be the most significant advance in the treatment of diabetes since the development of animal insulin for human use in the 1920's. The insulin synthesis is the first laboratory production of a significant, widely needed human hormone using recombinant DNA technology.

Recombinant DNA is the technique of combining the genes of different organisms to form a hybrid molecule. DNA (deoxyribonucleic acid), the substance genes are composed of, contains the chemical record in which genetic information is encoded.

(more)

Scientists at Genentech and City of Hope inserted synthetic genes carrying the genetic code for human insulin, along with the necessary control mechanism, into an E. coli bacterial strain which is a laboratory derivative of a common bacteria found in the human intestine. Once inside the bacteria, the genes were "switched-on" by the bacteria to translate the code into either "A" or "B" protein chains found in insulin. The separate chains were then joined to construct complete insulin molecules.

The development of the genetically engineered human insulin was funded by Genentech. However, the work was a cooperative effort between Genentech and City of Hope. The synthesis of human insulin gene was accomplished by four scientists at City of Hope Medical Center led by Roberto Crea, Ph.D., and Keiichi Itakura, Ph.D. Scientists at Genentech, led by David Goeddel, Ph.D. and Dennis Kleid, Ph.D., joined the genes that were made in sections and inserted them, along with the control mechanism into the E. coli bacterium. Arthur Riggs, Ph.D. at the City of Hope and Dr. Goeddel of Genentech were responsible for developing the final assays, purification and joining techniques.

Approximately 1.5 million diabetics take injections of insulin. At present, this insulin is extracted from the pancreas glands of swine and cattle slaughtered for food. It takes about 3,000 pounds of animal pancreas glands to produce one pound of insulin. The new process will produce ample quantities to meet the growing demand, and more importantly, produce a chemically identical human insulin.

(more)

One of the advantages of producing insulin using the recombinant DNA method is to reduce the dependency on animal glands. Also, by using insulin that chemically is identical to human insulin, scientists hope that certain allergic reactions by some diabetics to insulin derived from animals can be eliminated.

"The development of human insulin demonstrates the viability of using recombinant DNA technology to produce products with practical application," said Robert Swanson, president of Genentech.

"While extensive testing and refinement of the process is needed, we want to see human insulin and other genetically engineered products benefiting the people who need them in the shortest possible time," said Swanson.

Genentech, a privately financed corporation, and City of Hope have established a joint cooperative program to conduct basic research to develop commercial application of molecular genetic technology. Less than one year ago, Genentech announced its first product, the hormone somatostatin which was developed in a cooperative program with City of Hope Medical Center and the University of California San Francisco Medical Center.

####

## HOW THE HUMAN INSULIN WAS MADE

Insulin is a protein hormone composed of two chains of amino acids: an "A" chain and a "B" chain linked together by two disulfide bonds. The "A" chain is composed of 21 amino acids and the "B" chain of 30 amino acids, each arranged in a uniquely ordered sequence. (See Exhibit 1)

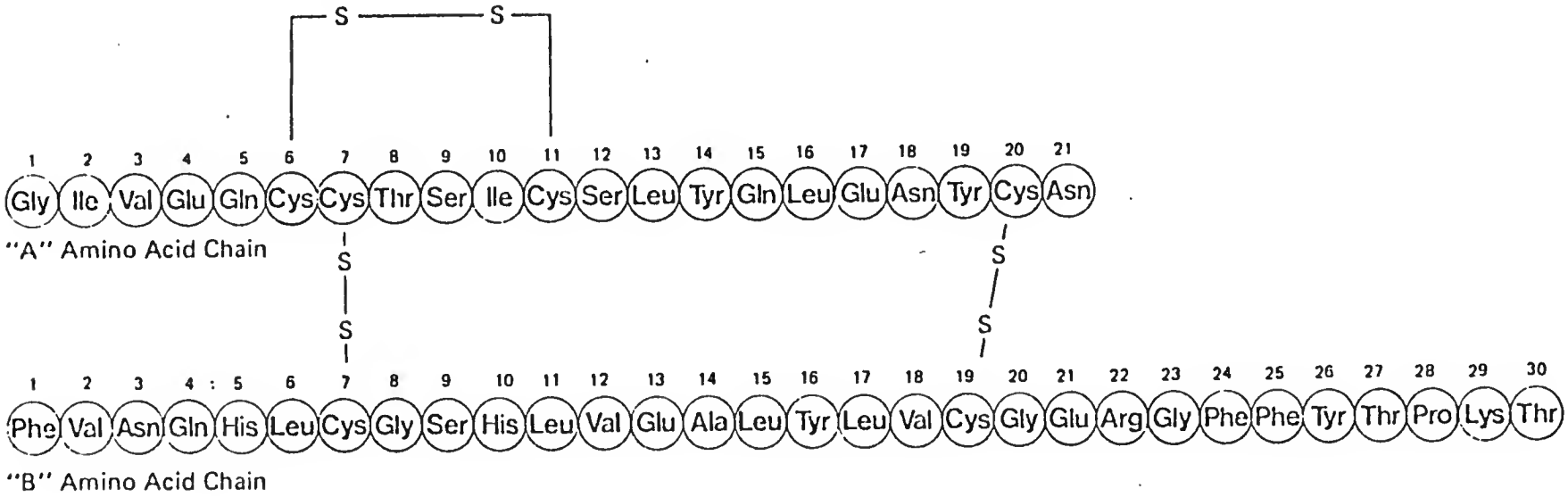
Proteins are made by translating the genetic information which is carried in a cell's genes. Scientists synthesized in the laboratory genes for the two insulin "A" and "B" chains. This was accomplished by chemically linking together small pieces of DNA sequence and then joining them in a specific manner to form complete genes. (See Exhibit 2)

Once the genes were synthesized, they were stitched into circular DNA strands called "plasmids" using special enzymes to perform the molecular surgery. Plasmids are rings of DNA which are found within the cell. The newly constructed plasmids containing the transplanted genetic material were introduced into a benign E. coli bacterial strain.

Once inside the bacteria, the genes were "switched-on" by the bacteria to translate the code into either the "A" chain or the "B" chain proteins found in insulin. The process is the same as that used by the bacteria to produce its own proteins. When the cells produced sufficient amounts of the "A" and "B" chains, they were harvested to isolate these proteins from the bacteria and purify it. The two chains were then combined chemically in the laboratory to form the complete Insulin molecule which is identical to that produced by the human body.

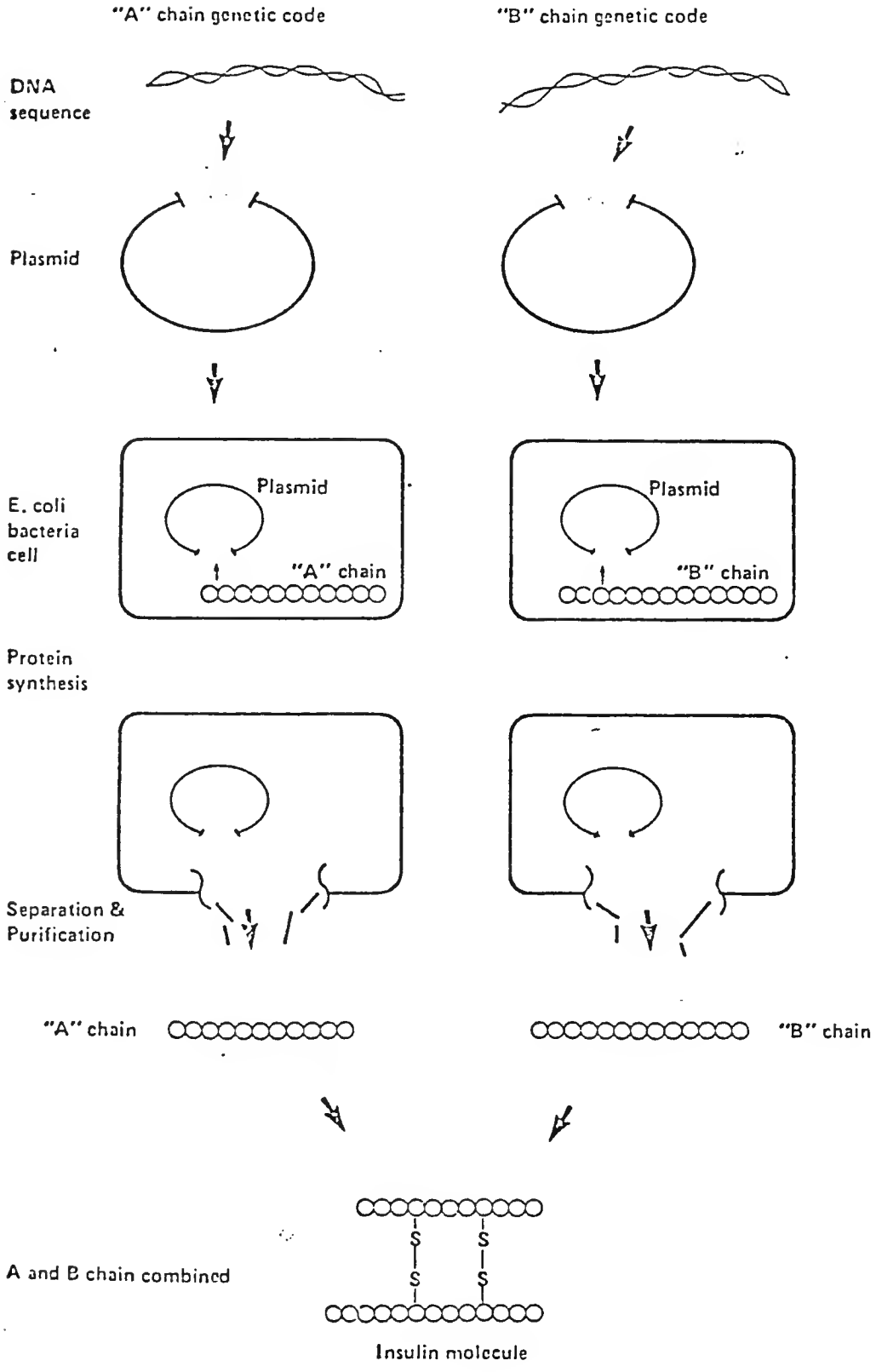
#

EXHIBIT 1. DIAGRAM OF A HUMAN INSULIN MOLECULE




| COMPARISON OF ANIMAL INSULIN AMINO ACID CHAINS WITH THAT OF HUMANS | | $A_8$ | $A_9$ | $A_{10}$ | $B_{30}$ |
|---|---|---|---|---|---|
| | Human | THR | SER | ILE | THR |
| | Bovine | ALA | SER | VAL | ALA |
| | Swine | THR | SER | ILE | ALA |

# EXHIBIT 2. DIAGRAM OUTLINING HOW THE INSULIN WAS MADE



# REPORT OF

# COMMITTEE ON RULES AND JURISDICTION

The Committee on Rules and Jurisdiction of the San Francisco Division of the Academic Senate met several times in response to the charge presented in a letter transmitted by Laurel Glass, Vice-Chairperson of the Senate to Sheldon Wolff, the chairman of the committee (see attachment).

The committee agreed to report to the senate on the matters in the charge as they pertain to any possible disruption of the academic functions of the university, i.e., the teaching and research functions of the faculty. It decided to think of the organization of Genentech and its relation with the campus only as an example of the type of contract that could lead to Dr. Glass's letter.

The first person to meet with the committee was Vice Chancellor Chater who assured us that the contract with Genentech had been examined by the general counsel of the university, was a legal contract, and conformed to university rules.

Before proceeding, the committee decided to ascertain for itself if the way in which the contract was carried out did indeed disrupt the academic function of the Department of Biochemistry where the work was performed. To this end, several people, ranging from senior full professors to an assistant professor, were interviewed. The committee met with Professors Bruce Alberts and Brian McCarthy who are acting co-chairmen of the department this year. Professor Herbert Boyer, who is the principal in the contract research, Professor Howard Goodman, who conducts similar research independently, and assistant professor Keith Yammamoto, who had been a postdoctoral fellow within the department and now was a junior faculty member.

With the exception of Professor Boyer, all believed that the manner in which the particular contract was carried out led to serious disruption within the department. Professor Boyer himself acknowledged that he was aware of the sensitivity provoked by the situation.

As the committee could reconstruct the situation, it seems that about four years ago Professor Boyer founded a company, Genentech, of which he is Secretary, a member of the Board, a major stockholder, and a paid consultant. The purpose of this company was to utilize recombinant DNA technology, of which Professor Boyer is a pioneer, to

manufacture various hormones and other pharmaceuticals. The company raised money and then let a contract to the university for work to be performed in Professor Boyer's laboratory for initial experiments to incorporate structures of DNA known to code for the desired proteins into plasmids so that the human gene products could be manufactured in bacteria. Experiments were to be performed to see if control of gene functions could be carried out, i.e., if the genes could be turned on and made functional. The resultant technology was to be patented by the university, which would receive 2% royalties in accord with its patent policy. Approximately one-half of this would revert to Professor Boyer and others who developed patents.

The principal representing Genentech in contractual matters dealing with changes in the budget, protocols of experiments, etc., was Robert Swanson, Genentech's President. The principal representing the university was Professor Boyer.

An exclusive license to use any patentable material was given by the university to Genentech. Because Genentech did not have any operable laboratories of its own, initially the experiments were carried out by Professor Boyer and two postdoctoral fellows in laboratories within the department. Mr. Swanson, in accord with the contract, would on occasion come to the laboratory and examine the laboratory notebooks. In addition, as a result of the publicity attendant with this research, television crews were in the laboratory on occasion.

The most serious matter heard by the committee was that this type of research, when carried out in a university environment, stifled academic communication. A recurrent theme was that people were loathe to ask questions and give suggestions in seminars, or across the bench for there was a feeling that someone might take an idea and patent it, or that an individual's idea might be taken to make money for someone else.

The situation is better now since Genentech has moved its research off the campus. Two of the persons interviewed expressed the opinion that the charge to the committee came two years too late, as earlier it was a very serious matter, but has since calmed down. The people interviewed were not unanimous in their appraisal as to whether or not there is a residue of disruption, but all agree the academic atmosphere is better than it was.

The committee believes that the problems attendant to this contract are likely to come up again in the future as biological research has more and more industrial worth. In the past, academicians in electronics, for instance, faced these types of problems and went out and formed their own

companies. This is a relatively new matter for biology. A large part of the unhappiness seems to stem from the philosophical perception of many basic scientists that pure research as carried out in the university should be altruistic, idealistic, and not pursued from a profit motive. It seems to many of these people that it is within the academic spirit to give freely of ideas and suggestions, if they are used to advance our knowledge (and even eventually to benefit mankind). It is not all right to do the same if another person is to make money out of it, even if by so doing he also helps mankind. The philosophical difference is extremely important as it goes to the heart of the idealistic beliefs of the purposes of a great university.

Not all of the faculty is that idealistic, however, and the committee believes that the situation was exacerbated by simple jealousy. The principals in the contract could possibly make millions of dollars, which is very different from the usual psychological rewards of peer acceptance in national and international scientific circles.

The committee believes that in order to carry out its function the university must keep its rules flexible enough to encourage the faculty to make professional contributions to society. Thus, the committee believes that there is no need to amend old rules or make new ones to cover contracts. It further believes that feelings of jealousy were intensified by the fact that the research was carried out by a person who is a paid consultant, as well as a major officer and stockholder of the company involved. In addition, those postdoctoral fellows who worked on the project were subsequently hired by Genentech at salaries considerably higher than those available to other postdoctoral fellows in the department.

The committee acknowledges that nothing illegal occurred and that all was in conformity with university rules. Furthermore, it believes that one cannot legislate against jealousy and other personal foibles in the faculty. Nevertheless, because a disruption in the academic functioning of a department did occur, and because this type of situation could possibly occur in the future as biological research begets the possibility of making large amounts of money, the committee urges that the existing rules be administered with an increasing sensitivity to the procedures that led to so much emotion in the present case. This should be done at all levels from that of the Chancellor's office and the Dean's office, down to the individual department chairmen who must be on the alert for situations that, even if legal, can disrupt the smooth academic functions of the departments. In a university the teaching and research and scholarly functions should take precedent over the functions of making contributions to public and professional service, as important as these latter two are. The

administration should be on the alert to contracts that could engender large scale serious jealousies on the part of its faculty. In respect to the latter, the committee believes that in the future it would be wise to refrain from making contracts in which work will be done by a university faculty member who also has a major financial interest in a concern, as this amounts to a contract between the person and himself, with the university's role only being incidental. This will become more important, as one can foresee situations where even more than one company is represented in a department. As more and more information is considered to be proprietary information, communication could completely cease, which is contrary to academic ideals and traditions.

One need for administrative action that should be taken now, concerns the confusion over inconsistencies in the rules regarding the retention of consultant fees and the confusion as to what is expected of the faculty in this regard. The committee notes that the clinical faculty can retain consultant fees in accord with an approved campus income assessment arrangement. The basic scientists in pre-clinical fields are not accorded the same privilege, in that the rule states that they shall not retain any net income from consultation (except federal governmental consultantships in the nature of service on grant and contract review committees). The strict full-time agreement signed by the basic science pre-clinical faculty has been ambiguous in this respect as it refers to "professional services" but not specifically to income from consultation. The committee believes that a uniform set of rules would prevent some serious jealousies that could develop, not only in regard to future contracts, but also in the general day to day functioning of the UCSF faculty. It further believes that, in some instances at least, the confusion and ambiguities accompanying the consultantship rules has led to their not being adhered to in their strict sense. It might be time to change the rules and drop some of the restrictions, especially as retention of such professional fees is acceptable according to university regulation 4 which states that the faculty may retain such consultant fees unless prohibited from doing so in the terms of their employment.

Respectfully submitted,

Sheldon Wolff

Sheldon Wolff
Chairman, Committee on
Rules and Jurisdiction

Members, Committee on Rules and Jurisdiction

S. Wolff, Chairman
T. Christie
P. Massey
R. Mitchell
T. Tozer
R. Creasy
M. Dunlap
J. Greene

## Economy & Business

# Investors Dream of Genes

*Genentech, a pioneer in daring DNA research, goes public*

The list of products by Genentech, a four-year-old San Francisco–based firm, reads like a cornucopia of blessings for mankind. It includes a hormone that may stimulate human growth, mass-produced human insulin that could reduce the cost of treating diabetes, and interferon (TIME, March 31), which may be used to treat everything from cancer to the common cold. Shares of Genentech are expected to go on sale soon on the over-the-counter market, and investors are queuing up to buy what some believe will be one of the strongest new issues of the '80s. A few brokers are already touting Genentech as the next Polaroid or Xerox. Says Financial Analyst Peter Smith of E.F. Hutton: "The expectations of the people doing research are mighty exciting. But for now we are selling sizzle —there is no steak around now."

ROGER RESSMEYER

**President Robert Swanson (left) with modern alchemists in their San Francisco lab**

*The company produces a chemical cornucopia for ills from the common cold to cancer.*

As Genentech itself states in its prospectus, the stock involves a high degree of risk. It is also likely to have a very high price-to-earnings ratio. The offering price is expected to be $25 to $30 per share, even though Genentech earned a meager 1¢ per share during the first half of 1980 for its private backers. The reason for all the excitement among analysts is that Genentech is one of four leading companies in the world doing recombinant-DNA research, a phenomenon that has had the scientific and investment communities elated for several years. Genentech is the first of the four firms to offer its stock to the investing public.

Recombinant DNA, or gene splicing, is a kind of modern alchemy. Scientists obtain DNA for a desired product, such as human insulin, and insert it into the DNA of a laboratory strain of a common intestinal bacterium. The bacterium, following directions from the new DNA, then produces the insulin. Scientists believe that the technique can be used to form a number of health-care, agricultural and industrial products more cheaply and easily than ever before (*see* MEDICINE).

There has been concern, however, over the safety of the new technique. At one point, researchers were so worried about the potential hazards of microbes' escaping from the laboratory and causing new illnesses that they formulated a set of safety guidelines to control experiments. These guidelines have been refined by the National Institutes of Health.

Genentech was founded in 1976 by Herbert Boyer, a biochemistry professor at the University of California at San Francisco and a pioneer in recombinant DNA, and Robert Swanson, a financier who finds backers for new companies. Almost immediately, the firm began announcing a series of breakthroughs. The first, in 1977, was the production of a brain hormone called somatostatin, which may be used to treat certain hormonal disorders. In 1979 the company developed thymosin alpha-1, which is now being tested by the National Cancer Institute for possible treatment of certain types of brain and lung cancer. Genentech's gross revenues have risen from $856,335 in 1978 to $3.5 million for the first half of this year.

With their success, Genentech's founders have also generated controversy in the scientific community. The company has worked closely with the University of California, sharing laboratory space and sometimes employees. When Genentech's manufacture of the human-growth hormone duplicated results published by university staff members, there were accusations that the company was secretly using the research. Genentech agreed last June to pay the university $350,000.

Other genetic-engineering companies have found large established firms to bankroll their research efforts rather than going to the stock market for capital. Berkeley-based Cetus, the oldest and largest of the firms, raised money by selling a microorganism it developed for penicillin production to Schering-Plough, a drug and cosmetic company. It also obtained backing from National Distillers & Chemical Corp. for a method to speed the manufacture of ethanol, which can be used with gasoline to make gasohol.

Genex Corp. of Rockville, Md., another fast-rising entry in the field, was founded three years ago by Molecular Biologist Leslie Glick and another professional raiser of venture capital, Robert Johnston. Though the company is secretive about its projects, Bristol-Myers revealed that Genex is working for it on the production of interferon.

Biogen S.A., which is based in Geneva, Switzerland, was the first firm to develop bacterial interferon. Founded in 1978, it is operated by a multinational board of directors and scientists. Schering-Plough last year invested $8 million in Biogen in return for exclusive worldwide manufacturing and sales rights to three of its products. Biogen has also found a second way to make interferon and is working on chemicals to cure foot-and-mouth disease, hepatitis and malaria.

Genentech, like the other major genetic-engineering firms, faces serious problems in profiting from its research. Obtaining approval for new products from the Food and Drug Administration is expensive and time-consuming. Notes Cetus President Peter Farley: "The lag time between discovery and marketing for a pharmaceutical product is five to 20 years." In addition, the four tiny DNA pioneers will be competing soon with such multinational giants as Du Pont, Upjohn and General Electric. Although the U.S. Supreme Court decreed this summer that new life forms could be patented, the U.S. Patent and Trademark Office has yet to rule on any of the 100 or so recombinant-DNA patents already submitted.

Thus while brokers are heralding the birth of a new growth stock, scientists are more circumspect. Says Walter Miller, a University of California researcher: "To buy stock in these companies right now would require an enormous leap of faith and an assumption about which company will be most successful." Nevertheless, investors are expected to rush to grab the first shares of Genentech. ■

MARCH 9, 1981 $1.50

# TIME

Prince Charles Picks a Bride

## Shaping Life in the Lab

### The Boom In Genetic Engineering

### Genentech's Herbert Boyer

10090 10
0 724404

## To Our Shareholders:

During 1981 Genentech continued to deliver on its promises, meeting both internal and contractural benchmarks. It was a fast-paced year for the Company. Four of the human pharmaceutical products developed by Genentech—human growth hormone, human insulin and two types of human leukocyte interferon—are now moving through various phases of clinical testing, the last stage prior to marketing. Two of our agricultural products—bovine growth hormone and foot-and-mouth disease vaccine—began their initial animal testing. Our scientists announced the development of microorganisms to produce six new products. We added further strength in management and began the expansion of manufacturing facilities that will accelerate Genentech's transformation into a company that both manufactures and markets the products of its own research.

*Operations*

In 1981, for the third consecutive year, the Company finished in the black, reaching its goal of operating at or near the break-even point in these start-up years. Seventy per cent of the Company's revenues came from operations—income from licensing or collaborative research and from product sales to industrial partners.

During 1981, our second reporting year since we went public, total revenues were $21.3 million compared with $9 million in 1980. Operating revenues increased to $15.2 million from $6.5 million in 1980.

As we have said before, until a number of Genentech's products reach the market in the next several years, we do not expect substantial earnings nor do we expect quarterly results necessarily to reflect accurately the progress being made during the year. There may be wide swings in quarterly results due to the timing of research benchmark payments. Because of the unpredictability of research and development, results do not come neatly packaged in three-month periods as do quarterly reports. For this reason a longer-term view will better measure Genentech's progress as we complete our transition to a fully integrated manufacturing and marketing company.

*Science*

The year brought increased awareness by the academic community of the high quality science under way at Genentech—in a corporate, for-profit environment. Our scientists published (after appropriate attention to patent issues) 31 papers in some of the best scientific journals. Broad interaction with other scientists and a continued flow of seminars and lectures at Genentech help to spawn a creative, innovative environment. The interaction among many scientific disciplines working together under one roof helped speed research results.

Our research was also extremely productive in generating new products. During the past year

*From left to right: David S. Tappan, Jr., David Packard, Robert A. Swanson, Herbert W. Boyer (standing), Thomas J. Perkins (seated) and Donald L. Murfin.*

our scientists announced the development of microorganisms to produce:

- Human immune interferon which many scientists believe may be the most promising of the interferons.
- Human calcitonin, a hormone important in the treatment of several bone diseases.
- Human serum albumin, a blood protein that can be used to re-establish normal vascular fluid levels after blood loss in surgery and accidents.
- Bovine and porcine growth hormones for accelerated weight gain by livestock and milk production by cows without the requirement of additional feed.
- A vaccine for foot-and-mouth disease so potentially important to the world's meat supply that U.S. Secretary of Agriculture John Block announced its development.

During the past year our scientists also refined earlier processes and developed new ones to allow us to maintain our development lead time. They have increased product yields, refined purification processes and made strides in industrial scale-up.

*Corporate Development*

By the end of 1981 Genentech had grown to a company with 318 employees. Ninety per cent of them are shareholders. Growth has continued with more than 350 employees now on board.

During the year we concentrated on building depth in management. We continued to fill out our organization at middle management levels with talented, experienced people carefully chosen for their ability to grow with the Company.

Two additions to our Board of Directors during the year also contributed significantly to our resources:

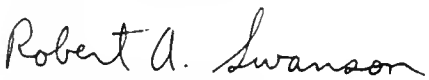
- David S. Tappan, Jr., is President of Fluor Corporation, a major engineering and construction firm. Fluor owns about four per cent of Genentech's shares. In 1980 Genentech and Fluor agreed to cooperate in exchanging technical information and to explore opportunities for developing scaled-up processes and design plants based on Genentech-developed technology.
- David Packard is Chairman of the Board of Hewlett-Packard Company, a leader in the electronics industry. Mr. Packard is a co-founder of Hewlett-Packard and played a key role in that company's successful transition from a small organization to its present eminence. From 1969 to 1971 Mr. Packard served as Deputy Secretary of Defense.

*An Eye on the Future*

Genentech is building the organization necessary to maintain our leadership position. Not only do we intend to remain outstanding in the development of novel microorganisms for production of new products, we intend to remain the best in scaling-up that production. Laboratory creation of a new product is the first step. It only begins to count when the product is purified and packaged. Our ability to move products through scale-up, GMP manufacture and clinical trials will be a key advantage for Genentech. Our strategy is being implemented with our investment in the construction of a new 72,000 square-foot manufacturing facility which will be completed in 1982. The new facility should provide us with the capacity to meet most of our production needs through the late 1980s.

This coming year, 1982, marks the beginning of our transition into the marketplace. In the future, contract payments will decline as a percentage of revenues, more and more of which will come from products manufactured and marketed by Genentech itself— thus capturing greater value from our substantial investment in research.

We are pleased with our shareholder support. We will continue to build value in our Company while focusing on the unique opportunity our technology provides.



Robert A. Swanson
President and Chief Executive Officer

Thomas J. Perkins
Chairman of the Board of Directors

March 17, 1982

UCSF NEWS
University of California, San Francisco

Carol Fox, News Director
Source: Robert Sanders (415) 476-2557

513 Parnassus Avenue Room S101
San Francisco, CA 94143-0462
(415) 476-2557
FAX (415) 665-8668

FOR IMMEDIATE RELEASE:
Wednesday, October 18, 1989

# PRESIDENT BUSH AWARDS NATIONAL MEDAL OF TECHNOLOGY TO UC SAN FRANCISCO'S HERBERT BOYER AND STANFORD'S STANLEY COHEN

WASHINGTON, DC -- UC San Francisco's Herbert W. Boyer, PhD, and Stanford's Stanley N. Cohen, MD, the fathers of genetic engineering, were awarded the National Medal of Technology by President George Bush today in a ceremony in the East Room of the White House.

Boyer and Cohen were cited "for their fundamental invention of gene splicing techniques, which allowed replication in quantity of biomedically important new products, and beneficially transformed plant materials."

The discovery of gene splicing technology, also called recombinant DNA, revolutionized basic biological research around the world, and has changed the face of biotechnology in this country.

The medal is awarded annually by the President of the United States to recognize individuals or companies that have made exceptional contributions to the well-being of the nation through the development or application of technology. Six other individuals also were honored at today's ceremony.

Boyer, 53, professor of biochemistry at UC San Francisco, and Cohen, 54, professor of medicine at Stanford University, first demonstrated the techniques of gene splicing in 1973, when they took genetic material from bacteria, recombined it with foreign genes, and introduced the "recombinant DNA" into other bacteria as hybrid chromosomes.

In 1976 Boyer joined with venture capitalist Robert Swanson to found Genentech, Inc., to bring the fruits of this revolutionary development to the marketplace. Genentech was the first and is still the largest gene splicing firm. Since its founding it has produced and is either testing or currently marketing genetically engineered human insulin, interferon, growth hormone, clotting factors and numerous other biological products.

(more)

mailed: 10/18/89 RSS:rsPmedtech

Today hundreds of biotechnology firms employ the Cohen/Boyer technique or similar techniques to produce drugs, hormones, vaccines and other useful products, and the technique is an invaluable tool in basic research labs throughout the world.

The citation accompanying the medal acknowledges as well "the innovative and aggressive patenting of this technology put in place by the University of California and Stanford University," which it says is expected to bring in royalties from around the world of $106 million by the time the patent expires in 1997.

Boyer was born in Derry, Pennsylvania, near Pittsburgh, on July 10, 1936. He received his undergraduate education at St. Vincent College, Latrobe, Pennsylvania, (BA 1958) and did graduate work in bacteriology at the University of Pittsburgh (MS 1960, PhD 1963). Following post-doctoral work in microbial genetics at Yale University (1963-66), he came to UC San Francisco in 1966 as an assistant professor of microbiology.

Boyer has received numerous awards and honors, including the prestigious Lasker Award for Basic Medical Research, which he received along with Cohen in 1980. He was awarded the V.D. Mattia Award of the Roche Institute of Molecular Biology in 1977, again with Cohen, and the two were elected to the California Inventors Hall of Fame in 1982. Both received the Moet Hennessy-Louis Vuitton Prize in 1988 from France's Institut de la Vie, and the first ever City of Medicine Award from the city of Durham, North Carolina and Duke University.

Boyer is a member of the National Academy of Sciences and the American Academy of Arts and Sciences. He was a Howard Hughes Medical Institute Investigator between 1976 and 1983, and currently is on the board of directors of Genentech, Inc.

Forty individuals -- including Boyer, Cohen and the six others who received medals today -- and one company have received the National Medal of Technology since it was first awarded in 1985. Recipients are recommended by a committee selected by the Secretary of Commerce, and the winners are chosen by the President.

###

UCSF NEWS
University of California, San Francisco

Carol Fox, News Director
Source: Robert Sanders (415) 476-2557

513 Parnassus Avenue Room S1
San Francisco CA 94143-04
(415) 476-25
FAX (415) 665-86

FOR IMMEDIATE RELEASE:
Tuesday, November 13, 1990

# GENETIC ENGINEERING PIONEER HERBERT W. BOYER AWARDED NATIONAL MEDAL OF SCIENCE

WASHINGTON, DC -- UC San Francisco's Herbert W. Boyer, PhD, co-discoverer of the gene splicing techniques that revolutionized biological research and sparked the biotech boom, was honored today with the nation's highest award in science, the National Medal of Science.

The medal was presented this afternoon by President George Bush in a ceremony in the East Room of the White House. A professor of biochemistry at UCSF, Boyer was one of 20 scientists to receive the medal. Ten other scientists and engineers were awarded the National Medal of Technology, which Boyer received last year.

The National Medal of Science is given annually by the President of the United States to recognize individuals for their contributions to knowledge in the physical, biological, mathematical, engineering, social or behavioral sciences.

Boyer, 54, and Stanley Cohen, MD, professor of medicine at Stanford University, first demonstrated the techniques of gene splicing in 1973, when they took genetic material from bacteria, recombined it with foreign genes, and introduced the "recombinant DNA" into other bacteria as hybrid chromosomes.

In 1976 Boyer joined with venture capitalist Robert Swanson to found Genentech, Inc., to bring the fruits of this revolutionary development to the marketplace. Genentech was the first and is still the largest gene splicing firm. Since its founding it has produced and marketed gentically engineered human insulin, growth hormone, and blood clotting factors, and is currently testing numerous other biological products.

Today hundreds of biotechnology firms employ the Cohen/Boyer technique or similar techniques to produce drugs, hormones, vaccines and other useful products, and the technique is an invaluable tool in basic research labs

(more)

throughout the world.

Boyer was born in Derry, Pennsylvania, near Pittsburgh, on July 10, 1936. He received his undergraduate education at St. Vincent College, Latrobe, Pennsylvania, (BA 1958) and did graduate work in bacteriology at the University of Pittsburgh (MS 1960, PhD 1963). Following post-doctoral work in microbial genetics at Yale University (1963-66), he came to UC San Francisco in 1966 as an assistant professor of microbiology.

Boyer has received numerous awards and honors, including the prestigious Lasker Award for Basic Medical Research, which he received along with Cohen in 1980, and the National Medal of Technology, which he received last year. He was awarded the V.D. Mattia Award of the Roche Institute of Molecular Biology in 1977, again with Cohen, and the two were elected to the California Inventors Hall of Fame in 1982. Both received the Moet Hennessy-Louis Vuitton Prize in 1988 from France's Institut de la Vie, and the first ever City of Medicine Award from the city of Durham, North Carolina and Duke University.

Boyer is a member of the National Academy of Sciences and the American Academy of Arts and Sciences. He was a Howard Hughes Medical Institute Investigator between 1976 and 1983, and currently is on the board of directors of Genentech, Inc.

Since the first medal was awarded in 1962, the National Medal of Science has been given to 284 individuals, including this year's honorees. Recipients are recommended by the National Academy of Sciences, and the winners are chosen by the President.

###

INDEX--Herbert W. Boyer

Åberg, Bertil, 89
Adelberg, Ed, 8-9, 11, 16, 17, 127
AIDS, 69
Alberts, Bruce, 97
American Society of Microbiology, 52-53
Arber, Werner, 12
Asilomar conferences on biosafety, 38, 43, 45-46, 51, 53, 54, 55, 112, 113, 122

bacteriophage, 15-16
Banting, William, 79
Bennett, Leslie, 66
Benzer, Seymour, 4
Berg, Paul, 32, 39, 42-44, 46, 60, 65, 71, 83, 84-85, 109
Best, Charles, 79
Betlach, Mary, 28, 45, 48, 62-63, 102, 111
Biochemistry, UCSF Department of. *See* University of California, San Francisco
Biogen, 103
biological warfare, 38
biosafety, 37-38, 42-46, 50-55, 56, 60-62, 63-65, 67, 69, 70-71, 78, 113-114, 122-123. *See also* NIH guidelines, recombinant DNA
biotechnology, technologies for, 121-122
Bishop, Michael, 20-22, 107
Bolivar, Paco, 48, 98
Boyer-Cohen recombinant DNA patents, 115-119
Boyer, Herbert W.
  awards, 83, 104
  collaboration with Cohen, 31-37, 103-110
  dissertation research, 3-4, 7-16
  Gordon conference, 1973, 39, 42-44, 102-103, 109, 118
  *Halobacterium*, research on, 49-50, 56
  protein-DNA interactions, research on, 56, 57-58
Boyer, Herbert W. *(continued)*
  UCSF laboratory, 119-121
  views on science, 49, 124-128
Boyer, Marigrace, 5, 6
Brinton, Charles, 7
Brown, Don, 39, 109
Brown, Wes, 41

Cal Tech, 73
Carlton, Bruce, 13
Caruthers, Marvin, 74
Cetus Corporation, 81-82
Chang, Annie, 30-31, 42, 105, 106, 111
Chargaff, Erwin, 11
City of Hope National Medical Center, 57-58, 73, 75, 78, 103, 104
Clark, John, 11,
Clements, John, 81
cloning research. *See* recombinant DNA
Cohen, Stan, 82, 83, 84, 125
  collaboration with Boyer, 31-37, 102-110
  recombinant DNA patents, 115-116
Comroe, Julius, 20
Crea, Roberto, 78, 103
Crick, Francis H.C., 2, 3
Crooks, Lawrence E., 81
crown gall research, 5-6
Curtiss, Roy, 113

Davis, Ron, 32, 85
Delbruck, Max, 16
d'Herelle, Felix, 15
DNA
  chemical synthesis, 57, 73-77, 78, 83, 121
  ethidium bromide staining, 31, 34-35
  fragment closure rates, 110-111
  radioactively labeled, 14, 31, 35
  sequencing, 32, 59-60, 109, 121
Dugaiczky, Achilles, 110
Dunphy, J. Englebert, 20

Edelman, Isidore, 20, 23
Eli Lilly & Co., 79-81, 88
Englesberg, Ellis, 1, 4, 6, 9
enzyme purification and characterization, 13, 14, 19-20
enzyme restriction and modification, 8-9, 11-13, 14-16, 31-37, 49, 109. *See also* restriction enzymes
Epstein, Charles, 25
European Molecular Biology Organization, 38

Falkow, Stanley, 31, 33, 52
Fredrickson, Donald, 62

gene mapping, 8-10
Genentech, Inc.
  benchmarks, 80
  business plans, 72, 87, 88
  corporate goals, 93-94
  corporate philosophy, 87
  development and scaling up, 94-95
  financing, 72, 79, 90
  foundation, 55, 71-73
  press conferences, 103-105
  publication policy, 87, 103-103
  staff recruitment, 77-78, 87, 91-92, 94
  stock, 73, 88, 92
  UCSF sponsored research agreement, 73, 89, 98, 101. *See also* growth hormone, insulin, somatostatin
genetic code, 3–4, 5, 74, 76
Gilbert, Walter, 57, 59, 60, 75, 78
Glaser, Don, 81-82
Glass, Laurel, 97
Goeddel, David, 74, 75, 77, 78 91-92, 104
Goodman, Howard, 54, 63, 78, 79
  collaboration with Boyer, 25, 27, 63, 106-107, 110
Goodman, Joel, 21
Gordon Conference on Nucleic Acids (1973), 39, 42-44, 102-103, 109, 118
Greene, Pat, 50
growth hormone, 72, 88-89
Guthrie, Christine, 68

Handler, Philip, 65
Havel, Richard, 20
Helinski, Donald, 47, 48, 112
Helling, Robert B., 31, 35, 40-41, 106, 118
Heyneker, Herbert, 48, 77-78, 91, 98, 101
Hopson, Janet, 60-61
Hubbard, Ruth, 52

insulin, 73, 75, 78-81
Itakura, Keiichi, 57, 58, 73, 75, 78, 104

Jawetz, Ernest, 16-17, 18-19, 21, 28
Jonsen, Al, 67

KabiGen, 79, 88
Kaiser, Dale, 84
Kerr, Clark, 20
Khorana, Har Gobind, 74, 77
Kleid, Dennis, 77, 91, 104
Kleiner & Perkins and Associates, 72-73
Kornberg, Tom, 25
Krevans, Julius, 68, 97

laboratory infections, 6, 70-71, 123
Lamarckianism, 16
Levinson, Warren, 21
Levintow, Leon, 20-21
Luria, Salvador, 16

Maniatis, Thomas, 113
Martin, Dave, 68
McCarthy, Brian, 97
Mertz, Janet, 32, 85, 125
Meselson, Matt, 15
Microbiology, UCSF Department of. *See* University of California, San Francisco
microbial genetics, 1-3, 82
Miles Laboratory, 72, 114
Monod, Jacques, 96
Morrow, John, 31, 39, 42-43, 106, 109

Narang, Saran, A., 73-74
National Inventors Hall of Fame, 116
NIH guidelines for recombinant DNA research, 50-51, 52, 56, 60-62, 63-65, 67, 69, 70, 78, 113-114, 122. *See also* biosafety

Ofengand, Jim, 21

patents. *See* Boyer-Cohen recombinant DNA patents
plasmid
  distribution, 50
  pBR322 episode, 62-65, 122
  R&D, 5-6, 7-10, 14, 30-37, 46, 47-48, 69, 108-110, 111-114
Project Phoenix, 87
Ptashne, Mark, 112

Q Fever, 70-71

Ralston Retreat, 29
recombinant DNA
  and species barrier, 51-52, 111
  basic research, 27, 30-42, 55-57, 59, 74, 76, 84-85, 86, 121-122, 125
  commercial application of, 34, 41-42, 51, 71-72, 121-122. *See also* Genentech
  legislation, 122-123
  reagents, 114-115
  technology development & dissemination, 27, 46-49, 112-113. *See also* biosafety, NIH guidelines
Reimers, Niels, 115-119
restriction enzymes, 72, 85, 114-115, 125. *See also* enzyme restriction and modification
Rift Valley Fever, 123
Riggs, Arthur, 57, 58, 73, 75, 77, 104
Roberts, Richard, 115
Roche Institute of Molecular Biology, 104
Rosenberg, John, 57-58
Rowland, Bert, 116
Rutter, William, 22-24, 25, 26, 27, 28, 62, 63-65, 66, 74, 78, 79, 96, 122

Sambrook, Joe, 34
Sanger, Frederick, 60
Santi, Dan, 98
Scheller, Richard, 73
science in industry and academia, 92-93
scientific publicity, publication, 103-105
Sedat, John, 25
Sharp, Phil, 34
Shine, John, 60
Singer, Maxine, 43, 44
Sinsheimer, Robert, 51, 52
Smith, Lloyd "Holly", 20, 68-69
somatostatin, 65, 73, 75-77, 83-84, 87-88, 93, 103
Sooy, Francis A., 97
Spiegelman, Sol, 22
St. Vincent's College, 1, 2
Stadtman, Earl, 22
Stanford patenting & licencing office, 115-117. *See also* Boyer-Cohen patents
Stent, Gunther, 127
Stevenson, Adlai III, 63, 64
Stoeckenius, Walther, 49
Stroud, Robert, 49
Swanson, Bob, 71-73, 75, 77, 79, 82, 87, 90, 91-92, 94, 97-99
Syntex, 82

Tomkins, Gordon, 22-24, 112, 125
transposons, 11
Twort, Frederick W., 15

Ullrich, Axel, 61, 122
university/industry associations, 96-101, 103-105
University of California patenting & licensing office, 81, 116, 119. *See also* Boyer-Cohen patents

University of California, San Francisco
Academic Senate, 97, 99, 101
basic science at, 17, 20, 22
biosafety committee, 66-68, 97
Committee on Human Use, 66-67
Committee on Rules and Regulations, 97, 99, 101
Department of Biochemistry, 22-30, 49, 56-57, 74, 96, 123
Department of Microbiology, 16-22, 24, 27, 30
Division of Genetics, 25-26
P-3 facilities, 69-70, 123
press conferences, 103-105
University of Pittsburgh, 1-3, 5, 11, 12, 14, 31, 49, 50

Varmus, Harold, 21
Vinograd, Jerry, 41

Wade, Nicholas, 64-66
Wald, George, 52
Watson, Jim, 58
Watson, John, 98
Weinberg, Roger, 5
Wilson, Alan, 41
Wolff, Sheldon, 97

Yale University, 7-16, 17, 123, 125
Yamamoto, Keith, 97
Yanofsky, Charles, "Charlie", 8, 13, 17, 48
Yuan, Bob, 15

Ziff, Edward, 118

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. She received a Ph.D. degree in the history of science and medicine from the Royal Postgraduate Medical School, University of London, in 1972.

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

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