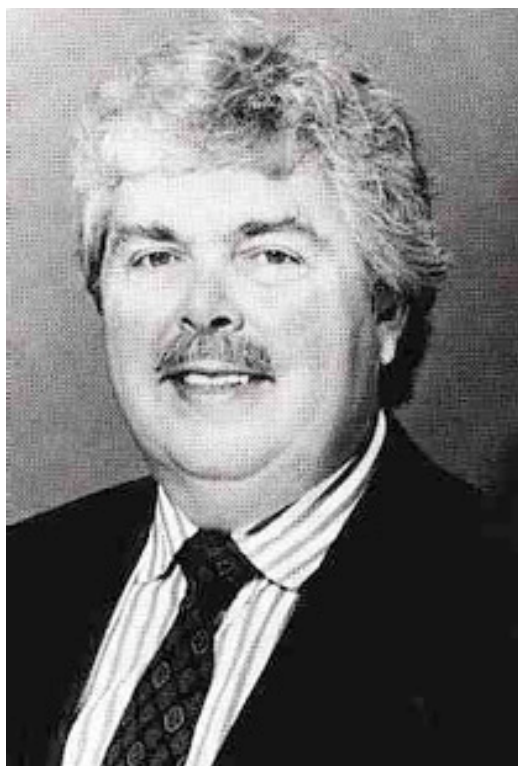


Interviews with
HERBERT W. BOYER PH.D.

RECOMBINANT DNA RESEARCH AT UCSF AND
COMMERCIAL APPLICATION AT GENENTECH



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DEPARTMENT OF ANTHROPOLOGY, HISTORY AND SOCIAL MEDICINE
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

PROGRAM IN THE HISTORY OF THE
BIOLOGICAL SCIENCES & BIOTECHNOLOGY
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INTERVIEWED IN 1994 BY SALLY SMITH HUGHES, Ph.D.
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INTRODUCTION

By J. Michael Bishop, M.D.

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 the 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 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 naïf. 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 naïve, 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 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 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; to the power of egalitarian opportunity, individual freedom, and noble ambition. And as the story is told here, it ends in a quintessential Boyersim: “So that’s about all I have to say.” It is said well and it should be read.

J. Michael Bishop, M.D., Chancellor, UCSF, September, 2001

INTERVIEWER'S INTERVIEW HISTORY

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 is celebrated for his development in 1973-1974, with Stanley N. Cohen of Stanford University, of recombinant DNA. In the business world, Dr. Boyer is remembered as a co-founder, with Robert Swanson, of Genentech, the first company founded on recombinant DNA technology. And in the legal field, he is associated with Boyer-Cohen patent of 1980 which set precedents for intellectual property in biotechnology. Although Boyer mentions the patent in this oral history, his interest lies in the basic science of recombinant DNA and the formation of Genentech.

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 what was 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 of the oral history 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, was settled on as Genentech's first project. There were some tense moments, as Robert Swanson's oral history dramatically describes. The cloning achievement, heralded internationally as evidence for the commercial potential of the new technology, 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.

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. Dr. Boyer's wife, a high school sweetheart, and devoted assistant Cookie Lupacchini were occasionally in the background. 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, thorough, and at times technical. His way of recalling past events made it apparent that science and its practical application remain a central

interest of his life. For reasons explained in the oral history, he has always kept his involvement at Genentech at arms 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, despite several requests. 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, which collaborates with UCSF and Stanford University in documenting these fields. The Boyer project was revived in 1998, as Nancy Rockafellar explains in her interview history. The oral history has been produced with identical transcripts but different accompanying pages in the UCSF oral history series and in the Bancroft Library's Program in the History of Bioscience and Biotechnology. I am grateful to Dr. Boyer for the time and energy expended on this project and to Cookie Lupacchini for graciously smoothing the way. I also thank the Genentech Foundation for Biomedical Science, which underwrote the interviews.

Dr. Boyer's modest and revealing account, when used with the oral history in progress 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.

Sally Smith Hughes, Ph.D., Regional Oral History Office, June 2001

EDITOR'S INTERVIEW HISTORY

Arriving at UCSF in 1966 as a new assistant professor with a strong interest in microbial genetics, Herbert Boyer was faced with teaching medical students on a campus with imposing clinical traditions. As this interview reveals from the perspective of a young researcher, the San Francisco campus in the mid-1960s was undergoing a transformation from clinical preeminence to a new focus on research in the basic sciences, a process catalyzed by Julius Comroe, Dr. Lloyd "Holly" Smith, Isidore Edelman, and Dean William Reinhardt with the support of UC President Clark Kerr.

The Department of Microbiology at UC San Francisco had, by the mid-1960s, a proud reputation for trachoma research and clinical evaluation of new antibiotics. As a young Ph.D. bench scientist, however, Boyer was more interested in bacterial pathogens in the older traditional microbiological sense. In this interview, Dr. Boyer reveals his personal disappointment over his cumbersome laboratory space and his gradual acclimatization as more sympathetic colleagues (Michael Bishop, Howard Goodman, Leon Levintow, Gordon Tomkins, and Bill Rutter) were recruited to UCSF basic science departments.

Throughout these recorded conversations, Dr. Boyer candidly reveals his thoughts and concerns, reconstructing the uncertainties that marked his early research career. He discusses his work in some depth, explaining the significance of practical aspects of the research, including the decision to use ethidium bromide stain, and selection of *Xenopus laevis* as an experimental eukaryote. As co-founder of Genentech, he provides crucial insider information on the nascent company's research, describing the work on somatostatin, and the use of chemically-synthesized DNA in the race to clone the insulin gene. He goes on to recount the details of his collaboration with Stanley Cohen and other scientists who contributed to the burgeoning field of molecular biology, careful to situate his own research efforts within the larger context. He comments freely on the contentious and financial implications of this new biology. Finally, he recalls the early struggle to launch Genentech, patent the rDNA technology, and the ambivalence surrounding university-industrial relations at the time. Throughout this remarkable firsthand account, Dr. Boyer carefully avoids hindsight and provides an intimate portrait of these most dramatic events in the development of biotechnology.

Technical Notes: This interview transcript was received from the interviewer in rough form in 1997 and the UCSF Oral History Program has double-checked the content of the ROHO transcripts with copies of the original taped interviews for accuracy. We have also added footnotes, section headings, a reference chronology, as well as an index and table of contents as aids to the reader and researcher. The designation in the manuscript "###" indicates that some text has been deleted for sense, but no large portions of this interview have been restricted or deleted by the editor or narrator. Text material in hard brackets has been added by the editor for clarity. Information provided in footnotes is identified by the initials of the contributor in hard brackets. This jointly published volume will now be placed in the UCSF Kalmanovitz Library and Berkeley's Bancroft Library and copies of the completed publication are now available through the Department of Anthropology, History and Social Medicine at UCSF, and the Regional Oral History Office at Berkeley.

Nancy Rockafellar, Ph.D., Director, UCSF Oral History Program
Department of Anthropology, History and Social Medicine
September, 2001

INTERVIEWS WITH HERBERT BOYER

INTERVIEWS MARCH 18 & 28, APRIL 7, & 20, JULY 22, 1994
 CONDUCTED BY SALLY SMITH HUGHES,
 EDITED AND ANNOTATED BY NANCY ROCKAFELLAR

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