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William J. Rutter, Ph.D.

THE DEPARTMENT OF BIOCHEMISTRY AND THE MOLECULAR APPROACH
TO BIOMEDICINE AT THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

VOLUME I

With an Introduction by
Lloyd H. Smith, Jr., M.D.

Interviews by
Sally Smith Hughes, Ph.D.
in 1992

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William J. Rutter.

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RUTTER, William J. (b. 1928)

Biochemist-biotechnologist

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Education; early career at universities of Illinois, Stanford, and Washington; research on galactosemia, aldolase, RNA polymerase, pancreatic differentiation; Department of Biochemistry and Biophysics, University of California, San Francisco [UCSF]: recruitment, development of department, introducing molecular approach, administrative and science strategy, collaboration and competition; director, Hormone Research Institute, UCSF; UCSF role in early biotechnology industry; Genentech; rat and human insulin gene projects; recombinant DNA controversy; biosafety; pBR322 plasmid episode; hepatitis B vaccine; commercialization of basic academic sciences; intellectual property; Gordon Tomkins; Howard Goodman; Axel Ullrich.

Introduction by Lloyd H. Smith, Jr., M.D., Associate Dean, UCSF School of Medicine.

Interviewed 1992 by Sally Smith Hughes for the UCSF Oral History Program, Department of the History of Health Sciences, University of California, San Francisco, and the Program in the History of the Biological Sciences and Biotechnology, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

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PREFACE

In 1990, the Department of the History of Health Sciences at UCSF, working closely with the UCSF Library's Archives, developed a formal Campus Oral History Program as an essential tool to document the oldest health sciences campus in the UC system. We were charged with the task of recording the postwar development of this unique institution, which rose from a good regional medical school in the mid-1960s to arguably one of the best medical schools in the nation. Oral History Program personnel quickly found that local stories represented important, hitherto undocumented landmarks in the development of postwar American biomedical science.

To provide fuller documentation of this institution's exemplary basic science programs, in 1991 Dr. Sally Smith Hughes was commissioned to begin a series of archives-based interviews covering the story of molecular biology and the university-industry relationships at UCSF. This volume represents the first of this series of interviews conducted with the pioneers of molecular biology and mediators of its commercial applications. The choice of Dr. William Rutter for the pilot interview is an obvious one, as readers of this interview will soon discover. His recruitment to UCSF in 1969 did much to create the entrepreneurial institutional environment for some of the most exciting developments in molecular biology and provided the catalyst for the nascent biotechnology industry. Other forthcoming interviews originally sponsored through UCSF's Campus Oral History Program include conversations with Dr. Herbert Boyer and Dr. Keith Yamamoto, scientists in UCSF's basic science programs. We gratefully acknowledge Dr. Rutter's generous participation in the arduous interview and editing process, and his role in the inauguration of an important series in the history of molecular biology and biotechnology in America.

Efforts are now underway to expand the initial charge of the UCSF Campus Oral History Program and conduct an exploration of the beginnings of molecular biology and biotechnology on several northern California campuses, using oral history interviews and collection of associated papers and records as essential tools. The future will bring expert collaboration among scholars, scientists, and archivists at UC Berkeley, UCSF, and Stanford, united in this important goal.

Nancy Rockafellar, Ph.D.
Director, UCSF Campus Oral History Program

San Francisco
March 1998

INTRODUCTION by Lloyd H. Smith, Jr., M.D.

It is a privilege to offer these few comments about William J. Rutter as the Introduction to this unique documentary of an extraordinary career. I do so in part from the perspective of a friendship of thirty years duration, but Bill Rutter has innumerable friends, personal and professional, from his many-faceted activities. The leitmotif of this brief essay will therefore focus more specifically upon his impact on UCSF as an institution in transition.

Among the more interesting philosophical speculations that recur in literature is the question of whether men create history by the sum of their acts of free will or whether the innate momentum of historic events creates men. No history of UCSF in the past generation would be complete without an analysis of Bill Rutter's seminal catalysis. Most of his academic colleagues, of whom I was privileged to be one, would concur that no other single individual played a more pivotal role in guiding the future of the institution during the past generation--in part, because of the importance of the position that he occupied as chair of the Department of Biochemistry and Biophysics, but more particularly because of his vision, vigor, and leadership of the whole of UCSF's basic science community. The details of those attributes emerge in the specific chapters that constitute this important history. It remains to place these compelling achievements in a larger context.

Henry Ford said, "History is bunk." Most of us, however, prefer the sonorous prose of Samuel Johnson, who, in Rasselas, wrote, "To judge rightly on the present we must oppose it to the past, for all judgment is comparative, and of the future nothing can be known. The present state of things is the consequence of the former, and it is natural to inquire what were the sources of the good that we enjoy, or the evil that we suffer. If we act only for ourselves, to neglect the study of history is not prudent; if we are entrusted with the care of others, it is not just." We are therefore justified to offer a truncated foray into history, to be both prudent and just, to understand the lineaments of "the good that we enjoy."

Founded in 1864 as the Toland Medical College, the UCSF School of Medicine is the oldest branch of the University of California as a continuing entity. Few in Berkeley are aware of that distinction. Like much of California, the School had a turbulent history, but unfortunately the perturbations were largely around a mean of mediocrity as judged by national standards. In his recent book concerning his tenure as president of the University of California, The Gold and the

Blue: A Personal Memoir of the University of California (1952-1967)¹, Clark Kerr has vividly described his analysis of UCSF after its first 100 years and his overall disappointment in its performance. This modest academic record stood out in sharp contrast against the continuing dominance of Berkeley in virtually all areas of scholarly pursuit, perhaps particularly in the physical and chemical sciences. In the late 1950s and early 1960s UCSF began slowly to emerge from a century of comparative somnolence. Among the many complex events in this emergence, the following can be identified:

- The return of the basic science departments from Berkeley to San Francisco to create, for the first time since 1907, a unified academic community;

- The rapid rise of funding for biomedical research from the National Institutes of Health;

- The construction of new clinical and basic science buildings--e.g., the Herbert C. Moffitt Hospital and the research towers;

- The move of the clinical activities of Stanford from San Francisco to Palo Alto. For the clinical departments this move opened up new opportunities at our affiliated hospitals;

- The development of an epicenter of excellence in the Cardiovascular Research Institute under the astute leadership of Professor Julius Comroe. It can be said that Julius Comroe was the proRutter of the 1950s, particularly in the physiological sciences.

- The gradual emergence of new leadership, beginning in the clinical departments, with national rather than regional ambitions.

These events occurred not without controversy, especially in the transitions in leadership at the levels of chancellor, dean, and departmental chairs. Some of this turbulence is described in Clark Kerr's memoirs, as noted above, and will not be revisited here.

In this oral history, Bill Rutter describes the events surrounding his recruitment as chair of the Department of Biochemistry and Biophysics (1968-69). He cannot be fully aware, however, of the long gestation period and the dystocia that culminated in the birth of this new era. Our Department of Biochemistry and Biophysics at that time was rightly perceived at the national level as lacking in both prestige and resources. As chair of the search committee, I presided over a prolonged and wearisome search during which many of the then recognized national leaders in the biochemistry of that day were approached as candidates for this position. Always we were rebuffed, but were often able to use this failure to advocate the assignment of more resources from the administration to this key department. I do not now recall how we learned more than thirty years ago that hidden in the rain forests of Seattle, along with Hans Neurath and the spotted owl, there was a

¹The University of California, forthcoming.

promising young investigator who was doing imaginative work on the development and function of the pancreas. His credentials on review seemed impeccable, although marked by a remarkable propensity for peregrinations--Idaho, Harvard, Utah, Illinois, Wisconsin, Stockholm, Illinois again, Stanford, University of Washington. The details of these fruitful wanderings are once again documented in this history. We decided to take a chance on someone who was considerably younger and, at the time, less eminent than our previous candidates had been--and, fortunately, he decided to take a chance on us. With him as a "package" came the late Gordon Tomkins, who himself had been a candidate for the chairmanship but with his usual penetrating intelligence saw in Bill Rutter the ideal leader for the future of the Department of Biochemistry and Biophysics.

Leadership is difficult to define but easy to recognize in action. There is no single style that makes effective academic leadership, which has been defined as the singular ability of an individual to stand up and pull the rest of us over the horizon. Suffice it to say that the arrival of the Rutter-Tomkins team almost immediately began to transform the climate of the whole basic science community at UCSF. New standards of performance were both exhibited and demanded. Bill had then, and still retains, an innate and uncanny ability to judge people. It has been said that horse sense is the good sense horses have not to bet on people. But academic leadership depends, in considerable measure, in betting on people, especially during the ascending curves of their respective careers. The appointments in Bill's department were astutely made and many of these individuals remain today as leaders of our campus.

Fortunately, Bill Rutter fostered lateral dendrites as well, such that UCSF's whole basic science community synaptically improved in parallel with the transformations that were so evident in the Department of Biochemistry and Biophysics. Many of these campus improvements came through simple suffusion of the newly established standards of performance. Others came through more formal arrangements, such as the Program in Biological Sciences. PIBS has served as a permease among departments and organized research units not only in graduate education but in research collaborations as well. Based on the striking success of PIBS, an analogous program was established at UCSF in the more integrative sciences. As a result of these initiatives, and the uniquely talented group of investigators who were attracted in those early heady days of change, the model for UCSF science was established--small laboratories, elite participants, highly interactive research; a philosophy strongly supportive of the individual scientist as opposed to large research teams. I shall not attempt to list here the remarkable group of scientists who were attracted to San Francisco as participants in this nationally recognized transformation. Many of these names are woven into the recitation of this oral history. Notably, Bill Rutter's interests transcended the boundaries of his own department and even the

community of the basic science faculty. His balanced judgment was called upon to help guide the growth in size and quality of the whole UCSF academic health science center.

It has been said that a central tragedy of life is that generally by the time you've made it, you've had it! Not so with Bill Rutter who has developed a second distinguished career as a pioneer in biotechnology. But with his departure from our institution on Parnassus Avenue, Bill Rutter's interest in and influence on UCSF's future have not been attenuated. He has been the major impetus behind the organization of the Bay Area Life Science Alliance (BALSA). Through this entity, of which he serves as chairman, Bill Rutter is at the forefront in shaping the future of UCSF at its new Mission Bay site. Few would deny that this is the single most important development for UCSF in the last half century.

Thomas Hobbes defined curiosity in this quaint manner: "Desire to know why, and how, curiosity, which is a lust of the mind, that by a perseverance of delight in the continued and indefatigable generation of knowledge, exceedeth the short vehemence of any carnal pleasure." Throughout his career, Bill Rutter has exhibited an unabated lust of the mind. UCSF has been and remains the grateful beneficiary of that lust. The Greek concept of happiness was: the exercise of vital powers along lines of excellence in a life affording them scope. Anyone who reads this account will quickly encounter vital powers, excellence, and scope constantly displayed.

Lloyd H. Smith, Jr., M.D.
Associate Dean
UCSF School of Medicine

November 1998
San Francisco

INTERVIEW HISTORY--William J. Rutter, Ph.D.

William Rutter's oral history inaugurates a series begun in 1991 under the auspices of the Department of the History of Health Sciences, UCSF, and continued at the Bancroft Library, UCB, as the Program in the History of the Biological Sciences and Biotechnology.

Dr. Rutter was a logical choice to initiate the first three oral histories, all with members of the Department of Biochemistry and Biophysics at UCSF.¹ As chairman from 1969 to 1982, he is credited with starting the department on the path to its current first-rank position in biochemistry and for spearheading UCSF's rise to prominence in biomolecular science.

The situation was far different when Rutter assumed the chairmanship in the late 1960s. He was confronted with a moribund department that had been without a chairman for six years and a faculty engaged in research in classical biochemistry. "Probably every good scientist in the United States," as he put it in the oral history, "had been asked to take that job. Sooner or later all those asked turned it down." In fact, Rutter himself rejected offers three or four times. A deciding factor in his change of mind was the twenty open faculty positions, which he saw as a bonanza for recruiting top-flight scientists who espoused his molecular view of science. It was a view buttressed by a few farsighted individuals on campus--Holly Smith in Medicine, Bert Dunphy in Surgery, Stuart Cullen Dean of the School of Medicine--who recruited Rutter as the prime architect of a coordinated, molecularly oriented basic science program. They wished Rutter, and those to be recruited after him, to transform a mediocre, clinically oriented school of medicine into an institution in which the "New Biology" suffused the clinical sciences. "New" of course meant molecular.

Rutter, a biochemist, was an attractive figure because of his research on RNA polymerase and other enzymes, and his interest in building a multidisciplinary research approach to the biology of eukaryotes, that is, "higher" organisms with nucleated cells. Molecular biologists to that point had largely focused on "lower" organisms, particularly the bacterial viruses and bacteria. Rutter was also seen as possessing the energy and vision to accomplish the multilevel task of building a cooperative research enterprise for the school as a whole. Departmental walls were to be figuratively torn down and fruitful interdepartmental collaborations to be encouraged, particularly between basic and clinical scientists. Despite pervasive sentiment to the contrary, Rutter and his supporters were set to prove that top basic science could be conducted in a medical school setting.

¹ The others are Herbert W. Boyer and Keith R. Yamamoto.

The going was not easy, as Rutter recounts in the oral history. Dead wood had to be tactfully cleared, contiguous physical space garnered and maintained against predation, promising scientists attracted to a budding but uncertain endeavor, and internecine jealousies and squabbles settled or squelched.

Rutter is quick to emphasize, in the oral history and elsewhere, that he did none of this alone. He considers himself a team player--a team player, one might observe, as long as he is leader of the team. In the early 1970s, his closest ally was Gordon Tomkins, who was department vice chairman and a scientist seemingly known to everyone in contemporary biology for his idea-a-minute mind and engaging personality. He was also an accomplished classical and jazz musician, and, like Rutter, the leader of a large and ambitious laboratory group. The two formed a daunting team --Rutter, the strategic thinker and indefatigable leader, and Tomkins, the charismatic link to the leading lights in the basic and clinical sciences.

Rutter describes in the oral history how the two criss-crossed the country, canvassing the scientific scene for promising young scientists who could be convinced to adopt their multidisciplinary molecular attack on eukaryotic cell biology. It came to a tragic end in the summer of 1975 when Tomkins died after a brain tumor operation. The stunning impact of this personal and professional loss is detailed in the Rutter oral history as well as that with Keith Yamamoto, at the time a member of Tomkins' group.

It was in this period that Rutter and his colleague Howard Goodman launched a program to clone the genes for insulin--first the rat gene and later the human--using expertise and techniques largely available in the department. Perhaps most notable was the recombinant DNA technology developed in 1973 by Herbert Boyer at UCSF and Stanley Cohen at Stanford. Subsequent events brought triumph and turmoil: the Rutter-Goodman team's successful cloning of the rat insulin gene in 1977; the tensions generated by high-profile, cutting-edge research; an alleged violation of the NIH guidelines for recombinant DNA research; and the bitter controversy engendered by the rise of the biotechnology company Genentech within the department.

All this occurred against the backdrop of the international controversy over the possible hazards of recombinant DNA technology, the confusion engendered while federal guidelines for such research were being formulated, and the threat of federal and state legislation to regulate the new technology. The reader doubtless will be interested in Dr. Rutter's interpretation of these and other key events in the early history of genetic engineering.

The Oral History Process

These seven interviews were recorded between March and August 1992, either in Dr. Rutter's office in the Hormone Research Institute at UCSF, or

in the Office of the Chairman at Chiron Corporation, the biotechnology company that he co-founded in Emeryville, California in 1981.

With the exception of the first, the interviews were conducted on weekends when Dr. Rutter had slightly more flexibility in his frenetic seven-day-a-week, fourteen-or-more hour work days. His retirement from the university in March 1994 merely meant that he had more time to devote to Chiron and myriad other activities, including chairmanship of a fundraising campaign for a second UCSF campus, and membership on the Board of Overseers of Harvard University, his undergraduate alma mater. He has received several honorary doctorates and in 1995 the Heinz Award in Technology and the Economy.

Despite his pressing schedule, Dr. Rutter appeared relaxed and focussed on the interviews. Because of limited funding for the oral history, the interviewer was unable to conduct extensive preparatory research and hence had to rely largely on Dr. Rutter for the historical account. Thus, more than usual in this series, this is a history told from the narrator's viewpoint. Its emphasis is not on the details of scientific research, but rather on administration and strategies, institution-building, and entrepreneurialism.

The researcher interested in this history will want to consult Dr. Rutter's correspondence which, as a result of this project, is archived at the UCSF Library. Also relevant are the oral histories in this series with Herbert Boyer and Keith Yamamoto,¹ and others being conducted at the Bancroft Library on the history of molecular biology and biotechnology in California.² The various manuscript collections in the UCSF Library related to the School of Medicine, including some referenced in this oral history, provide additional information. Stephen Hall's book on the race to clone the gene for insulin includes extensive information on the Rutter laboratory and its competitors.³

As one might suspect, Dr. Rutter had difficulty in finding time to edit the interview transcripts. This volume represents a compromise; it contains the final version of seven of the twenty-five mostly short

¹ Yamamoto's correspondence, and that of several colleagues mentioned in the Rutter oral history, Bruce Alberts, Gordon Tomkins, and Harold Varmus, are also on deposit at UCSF Library.

² As of February 1998, interviews under the auspices of the Bancroft Library's Program in the History of the Biological Sciences and Biotechnology have been conducted with Paul Berg, Arthur Kornberg, Niels Reimers, and Robert Swanson.

³ Stephen S. Hall. Invisible Frontiers: The Race to Synthesize a Human Gene. Redmond, WA: Tempus Books, 1988.

recorded sessions.¹ Interview 10 was included in this volume because it addresses the subject of interview 6, the cloning of the rat insulin gene and the controversies related to it. Interview 6 was recorded before and interview 10 after Dr. Rutter provided testimony for the UCSF, Eli Lilly, Genentech insulin gene patent case. The remaining interviews, including seven through nine, will be available eventually as Volume II of the oral history.

Dr. Rutter edited heavily, in a few instances adding several paragraphs of new material. In most cases, although the syntax is improved, the content remains largely unchanged from the original transcription. As usually happens with extensive editing, much of the spontaneity of the original discussions has been lost, although they have without doubt gained in clarity.

The oral history program to document the history of molecular biology and biotechnology in the San Francisco Bay Area began at UCSF in 1991, when I was asked, as a science historian at the Regional Oral History Office of The Bancroft Library, to conduct three oral histories. Dr. Rutter's oral history was completed by the Bancroft Library's Program in the History of the Biological Sciences and Biotechnology. The Program's mission is to establish an integrated collection of research materials--primarily oral history transcripts, personal papers, and archival collections--relating to the history of the biological sciences and biotechnology in university and industry settings. The Program is presently focussed on the Bay Area and northern California, but its ultimate aim is to document molecular biology and biotechnology on the entire West Coast.

We gratefully acknowledge grants from Systemwide Biotechnology Research and Education Foundation, UCSF Library and Center for Knowledge Management, the Program in the History of the Biological Sciences and Biotechnology, and startup funds from the Office of the UC President through the UCSF Department of the History of Health Sciences. We thank Leslie Spector for providing background material and photographs.

Sally Smith Hughes, Ph.D.
Research Historian/Interviewer-Editor

Regional Oral History Office
The Bancroft Library
Berkeley, California
February 1998

¹ The remaining interviews on a wide range of topics, including hepatitis B research leading to the first recombinant vaccine and the foundation of Chiron Corporation, will be available after Dr. Rutter has reviewed the transcripts.

BIOGRAPHICAL INFORMATION

(Please print or write clearly)

Your full name William J. Rutter

Date of birth 08/28/28 Place of birth Malad, Idaho

Father's full name William Henry Rutter

Birthplace Liverpool, England

Occupation Merchant

Mother's full name Cecilia Dredge Rutter

Birthplace Malad, Idaho

Occupation Homemaker

Where did you grow up ? Malad, Idaho

Present community San Francisco

Education Ph.D. 1952 University of Illinois/Biochemistry
M.S. 1950 University of Utah

B.A. 1949 Harvard University/Biochemistry

Occupation(s) Professor Emeritus, Department of Biochemistry & Biophysics,
University of California, San Francisco
Chairman, Chiron Corporation, Emeryville, California

Special interests or activities _____

I EDUCATION AND EARLY CAREER

[Interview 1: March 3, 1992] ##¹

Early Education

Hughes: Let's start with where you were born and educated.

Rutter: I was born in Malad, a little town in southern Idaho. I went to school through high school in Malad until I was fifteen or so. I left early and attended BYU [Brigham Young University] in Utah for one year. Then I more or less lied about my age to join the navy. When World War II ended I got out and went to Harvard; majored in chemistry and biochemistry.

Hughes: Did you have any idea of what you wanted to do?

Rutter: No, none at all. But Harvard is a great university and a marvelous place to get an education. At that time, and probably now, it was quite possible to concentrate in one area and be educated in another. So though I took lots of classes in science, I also attended many classes in history and art and the social sciences. It was a very good time for me.

Hughes: What pointed you toward science?

Rutter: It just became obvious early on. I like mathematics and I like technical things. My grandfather had been a British army officer in India, so I became interested at an early age in parasitic diseases. During high school, I did a lot of reading on parasitic diseases.

Hughes: Was your grandfather a medical man?

¹ ## This symbol indicates that a tape or tape segment has begun or ended.

Rutter: No, but India was rampant with medical problems. It was exotic and full of poor and rich, but dominantly poor, and all these absolutely fascinating diseases which, in one way or another, he described to me.

I wanted to go to the School of Tropical Medicine in Calcutta. Hence, I was more or less interested in that subject but I had a rather diffuse and not well-formed set of ideas.

Hughes: But you were thinking of medical school?

Rutter: Yes. When I was at Harvard as an undergraduate, I did some research with Avram Goldstein, who later became head of the Department of Pharmacology at Stanford. Goldstein was an extremely fine scientist, and I benefitted greatly from reading his papers and learning of his research first hand. Goldstein was at the medical school; I was at Harvard College, so I traveled from Cambridge to Longwood Avenue in Boston by streetcar. I had a lot of good feelings about the problems of clinical science. That led me to apply to medical school.

When I graduated--I graduated in the middle of the year [1949]--I was going to medical school. I had been accepted into medical school at Harvard and I was going to return. But for the intervening time, I came home to be nearer to my family. I went to some of the medical school classes at the University of Utah in Salt Lake City where a cousin of mine had been going to school. I also did some research there. After a short period, I decided that medical school was not for me, that I was going to go into research. So, I stayed on for another year with Gaurth Hansen [in the biochemistry department at the University of Utah Medical School] who was a great person to work with, and I received an M.S. degree [1950]. Gaurth eventually left to go to the University of Illinois and I went with him as a graduate student.

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Hughes: Was the reason for giving up medicine because you were fascinated by biochemistry?

Rutter: Yes. I didn't like the lack of real understanding in medical courses, and the practice of medicine. I liked all the basic science courses, such as chemistry, biochemistry, pharmacology, physiology, and I was drawn to research. I guess the collision of those two interests put me eventually at the interface between science and medicine.

Doctoral Student, University of Illinois ##

Hughes: What were you and Hansen doing?

Rutter: We were doing metabolic physiology on rat tissue, trying to understand metabolism.

Hughes: He was a physiologist?

Rutter: No, he was a biochemist. But then the emphasis of biochemistry was on metabolism and metabolic pathways.

I ended up doing my degree on a metabolic disease called galactosemia in which the human becomes intolerant of lactose and galactose--mother's milk contains lactose.¹ Lactose is composed of normal sugar, which is glucose, attached to this rather unusual sugar called galactose. Some people are intolerant of galactose, especially children. They become mentally deficient and have hepatomegaly, that is, enlarged liver. Galactosemia is a severe disease.

Hughes: Galactosemia was an interest of Hansen's?

Rutter: Not really. Gaurth knew a great deal about carbohydrate metabolism but I became interested in galactosemia more or less by myself. It was just when my son was born. I had a quick conversation with the pediatricians, about pediatric diseases, and I decided to work on galactosemia, which is caused by a deficiency in one of the enzymes involved in the conversion of galactose to glucose.

The Decision to Study Biochemistry

Rutter: The end of my interests in galactosemia is kind of interesting. It is very difficult to get human patients in which to study this disease, but one can produce a model of the disease in chickens. In fact, if one feeds lactose to baby chickens, they develop a remarkable syndrome in which, when disturbed or in any way excited, they flutter around the cage uncontrollably and, in an incredible tonic convulsion, become stiff as a board for several

¹ For references to research mentioned in this oral history, the reader is referred to Dr. Rutter's bibliography in the appendix.

minutes and then relax. After several minutes, they are subject to the same thing again and again.

We showed that feeding galactose led to the accumulation of peculiar lactose-containing compounds both in the serum and the brain tissue. We also did experiments in bacteria which could only use lactose--they couldn't grow on glucose or galactose. We expected that there might be a special enzyme involved in metabolism of lactose. However, it turns out that those bacteria have a transport system which selectively brings lactose into the cell. That was one of the earliest studies of special transport molecules, in this case the lactose transporter. In this instance the transporter accepts lactose but not glucose or galactose. This work was done by Herman Kalckar, a famous Danish scientist then at Harvard. We didn't really get to understand galactosemia by the bacterial model. Gaurth Hansen spent much of the rest of his life working on this problem, eventually in human beings.

Postdoctoral Fellow, University of Wisconsin Institute of Enzyme Research, 1952-1954

Rutter: I got into two interesting aspects of science in my graduate training. Illinois had one of the best departments of chemistry in the U.S. I wanted to move on rapidly, so I got my Ph.D. degree in three years [biochemistry, 1952]. Then I went to Wisconsin where I studied enzyme chemistry with a well-known scientist named Henry Lardy, who was at the enzyme institute, a quite famous place for studying enzyme and metabolic pathways.

Hughes: Is that why you had gone there?

Rutter: Yes, I wanted to learn more about proteins and enzymes. I worked with Lardy on a problem involving the characteristics of an enzyme, the malic enzyme, that was fascinating to biochemists because it was involved with carbon dioxide fixation in animals. Carbon dioxide fixation is a process which is normally associated with plants and requires light. But it had been shown by Harland Wood that carbon dioxide fixation can occur in other cells. So this was a study of an enzyme that carried out carbon dioxide fixation and fed the products into the central metabolic cycle (the Krebs tricarboxylic acid cycle) that occurs in most cells that derive metabolic energy from oxygen.

Hughes: How did you end up with that project?

Rutter: Henry Lardy was very much interested in the metabolic pathway, and I was interested in learning about enzyme chemistry, so it was just a vehicle for understanding.

While I was involved in the malic enzyme project, I became interested in the mechanism of another enzyme that was being studied in the lab. This enzyme, aldolase, carried out a reaction which was very similar to a classic organic chemical reaction, for which the organic mechanism was largely known. Of course, the enzymatic mechanism was not known. In fact, no enzymatic mechanism was known. I was fascinated to learn whether the enzyme acted as a classic base. (The organic reaction was base catalyzed.) I predicted that if this were so, the enzyme would catalyze an exchange reaction of a carbon-bound hydrogen with water. If the enzyme reacted specifically, the reaction should be stereospecific. (There were two hydrogens on the carbon involved in the aldol condensation.) Such reactions had not been observed in biological systems, and Henry Lardy and others thought the idea was far-fetched. However, the more I thought about it, the more I wanted to carry out the experiment.

Hughes: You had worked out the concept theoretically?

Rutter: Yes. I made an agreement with Henry Lardy that I could work weekends on this problem. It turned out that the enzyme did catalyze a stereospecific hydrogen exchange reaction. At that time, we didn't have radioactive hydrogen (tritium) to measure the exchange reaction. We had to use nonradioactive deuterium, so it was a complex analysis. The data were very convincing. That was my first great pleasure in science.

After this result, I decided to study the mechanism in greater detail. It turned out that a famous scientist in Sweden named Hugo Theorell (who later won the Nobel Prize for other work) had carried out studies with Linus Pauling using techniques that might demonstrate the details of the mechanism. It was possible that an enzyme-bound metal ion might be involved in the reaction. Another Nobel Prize winner in Germany, Otto Warburg, had provided evidence that aldolase in yeast required an iron atom. If iron were involved in the reaction, the mechanism would probably have involved changing the valence state of the iron atom with a consequent change in magnetism. Theorell had developed a kind of "magnetic balance" which appeared to be able to measure the difference in magnetic charge between the valence states of iron.

Postdoctoral Fellow, Biochemistry Department, Nobel Institute,
Stockholm, 1954-1955

Rutter: In all my conversations with Theorell and all my writings to him, it seemed as if the experiment was feasible. Therefore, I picked up my family and left Madison and went to Stockholm to do these experiments. It turned out that the magnetic balance wasn't sensitive enough. We would have required several kilograms of this enzyme (a prodigious task). More importantly, it turned out the enzyme wasn't a metallo-enzyme after all. Further, I found out that the yeast enzyme was not an iron enzyme as Warburg thought, but a zinc protein, and zinc had no magnetic properties. Thus there seemed to be two fundamentally different types of aldolase carrying out the same reaction. This was a truly unusual situation. It had been thought that evolution created only one solution to a single problem. Clearly there were two. I became interested in the two mechanisms and their functions in evolution.

Hughes: It was far from a wasted year.

Rutter: It was a great year. I learned a lot of things. I spent a year there and then met another scientist, Professor Theodore Bucker from Marburg, Germany, who also was interested in enzyme mechanisms.

Hughes: Was this a popular field?

Rutter: Enzyme chemistry was at the heart of biochemistry, but it was just the beginning of mechanistic studies of enzymes. Among biochemists, it was avant-garde; there weren't many people involved. One of these was Emil Smith, who was on the faculty at Utah when I was there, who then moved to UCLA to be head of the Department of Biochemistry there. Dan Koshland at Berkeley was another. Most scientists were characterizing the enzymatic properties, not revealing their mechanisms or actions.

At that time, scientists tried to understand the catalytic process in terms of the rates of the various steps of the reactions, on-off of substrates, and the role of the functional groups of the enzymes at the active site. Studies involved the chemical modification of the substituent groups, but these studies were compromised by the lack of specificity of most chemical reagents used to interact with the enzymes. Studies of a reaction involving metal at the active site held some advantages because its actions could frequently be clearly investigated. Furthermore, studying two different mechanisms for the same reaction had some real advantage.

Assistant Professor to Professor, University of Illinois, Urbana,
Division of Biochemistry, Department of Chemistry, 1955-1963

Return to Illinois

Rutter: Then I came back to the University of Illinois in the biochemistry division of the Department of Chemistry.

Hughes: Why Illinois?

Rutter: Well, at that time I had two choices, a chance to go to Stanford in the biochemistry department headed by J. Murray Luck, or to Illinois where I obtained my graduate degree. I chose Illinois because the chemistry department was a great department, one of the two or three best departments in the country. (E. J. Corey later moved to Harvard and got a Nobel Prize.) The biochemistry division was part of that department and I had a lot of respect for the faculty there. Further, the Department of Microbiology was also a great department, with Sal[vadore] Luria, who later won a Nobel Prize, and Sol Spiegelman. [I. C.] Gunsalus was the head of the department and a former mentor of mine. For the sort of things I wanted to do, mechanistic enzymology on the one hand and extending my interests into biology, I was extremely fortunate. It was the right place at the right time for me.

Hughes: That was somewhat luck?

Rutter: Oh, yes. For sure.

Structure-Function Studies of Protein Families

Rutter: When I came back to Illinois, I started on two paths: one was the mechanism of enzyme action using the two aldolases as paradigms, supplemented by a strong interest in the development and conservation of catalytic mechanisms (enzyme families) in evolution. These two interests could be simplified to structure-function studies of protein families. Metabolic pathways are comprised of a few common mechanisms applied to different substrates. The aldolases types I and II represented two evolutionary distinct solutions to catalyzing C-C [carbon-carbon] bond cleavages and ligations. There are probably more than 100 different enzymes carrying out these reactions. One subfamily is metallo-enzymes using zinc as a fundamental nucleophile. Class II aldolase involves the formation of a Schiff's base with a lysine

group of the enzyme. These two mechanisms were quite pervasive in all biological systems.

After spending some years working on enzyme mechanisms, I became convinced that the ultimate goal of understanding the mechanisms of these enzymes, beyond identification of residue involved, was not possible at that time because of technical limitations which I could not solve. Thus I decided to reduce my concentration on structure-function and concentrate more on biology where knowledge was more primitive, but where there was great potential.

Hughes: What were you thinking of when you said "technical limitations"?

Rutter: The point is that to understand enzyme reaction mechanisms, you have to know the structure of the so-called transition state, that is, what's happening during the catalysis itself. The rates are very fast. You go through the transition state, from reactants to products, several thousand times a second. In order to understand the structure of the transition state statistically and dynamically, one has to have chemical or physical tools which were just not available. One had to employ indirect methods and do experiments which stopped short of being decisive. Some of these tools became available in the late 1980s. With the rapid development of molecular genetics, the genetic code, and the transcription/translation process, biology was more attractive.

Research on Aldolase

Rutter: I didn't give up on aldolase and enzyme chemistry. In fact, we discovered different subtypes of aldolan all carrying out the same reaction and performing with a Schiff base intermediate subtly different physiological functions in muscle, liver, and brain. A characterization of the liver aldolase (aldolase B) and its role in fructose intolerance is just now being clarified by the students of my former students.

We also became involved in a controversy about the subunit structure of aldolase. A number of major labs had become interested in a subunit structure of enzymes, first from the genetic point of view (how many genes are required to encode an enzyme?), also from the chemical view (do multimeric proteins confer special properties on the molecule that are not possible with monomers?), and finally biologically (is the diversity of catalysis or substrate specificity in a major way determined by multimerization?).

Much of the early work on this subject focused on hemoglobin, and the role of subunits in determining its different properties for binding oxygen--[Jacques] Monod and [Francois] Jacob at Institut Pasteur, [Jeffries] Wyman and [John] Edsall at Harvard, etc. It was found that aldolase was a multimeric protein. Many labs, including [Bernard] Horecker is at [Albert] Einstein [College of Medicine], [Paul] Boyer is at UCLA, [Howard] Schachman at Berkeley, determined structure by analyzing the number of C [carbon] termini; the number varied around three. This would have been the first trimeric protein so there was much interest in this point. I became convinced that there were too many sources of error to obtain a decisive answer to this question by chemical analysis.

We devised a method to solve this problem by combinatorial analysis, i.e., through the formation of hybrids. If one mixed the subunits of aldolases A and B (the subunits of A and C have distinguishable properties), then the number of hybrids formed would depend on the number of subunits, i.e., if there were three subunits there would be four hybrids (A_3 , A_2B , AB_2 , B_3). However, if there were four subunits, there would be five hybrids (A_4 , A_3B , A_2B_2 , AB_3 , B_4). One could easily determine the number of hybrids, either as they existed naturally in cells (where both enzymes were synthesized in the same cell), or artificially by recombination. Experiments clearly showed there were five hybrids formed, therefore four subunits. The answer could not be disputed.

For our work on aldolases, I was given the Pfizer Award in Enzyme Chemistry [of the American Chemical Society's Division of Biological Chemistry], in 1967. At that time I decided to stop working on this problem. Several of my students, Ed Penhoet primarily and Herbert Lebherz, continued to work on these enzymes to study their structure and function. The genes for aldolase were finally cloned in Penhoet's lab in the late 1980s.

This ended a chapter in my scientific life. I had spent ten to eleven years working on aldolases, carrying out a set of studies using a molecule as probe. Chemistry, genetics, biology, and evolution--as the philosopher Francis Bacon said, each one of us sees the universe in his own grain of sand.

Early Studies of RNA Transcription Regulation

Rutter: I was still very interested in enzyme mechanisms, but I always thought more or less along biological lines. This was a few years after the discovery of DNA [structure, 1953], during the time when

genetic expression was being intensively investigated in big labs, the premier labs. Clearly this was one of the most fascinating new developments in all of science. It wasn't clear what the role of DNA was and what role transcription played in differentiation. DNA had to be transcribed. RNA and the codons were just being worked out by the major scientific figures of the time. What role could a young scientist with a small lab play? Stemming from my interest in enzymes, I decided to try to figure out the regulatory networks by which RNA transcription regulated and was regulated in biology.

Hughes: You had to pick up quite a bit of basic science that you hadn't dealt with before. Is that true?

Rutter: Oh yes. Of course. In all of these fields one learns "on the fly."

Hughes: How did you do that?

Rutter: Reading and talking to people, going to meetings, finding out what the major issues were, how they were being approached, where the field really was going, and who was leading it. I've always been very intense about science. In the end, I decided after doing some experiments in the laboratory with liver cells, that I would like to go to a place that had a great biological system and work awhile with an individual who was primarily a biologist but who was mechanistically or biochemically inclined.

Hughes: What do you mean by "a great system"?

Rutter: An embryologically developing system, a biological system which was susceptible to experimental analysis at the genetic and biochemical level. I was looking for an individual who was basically a phenomenologist who would define the system and tune it up, but who was not interested or didn't have the capability to begin to explore at the molecular level.

Eventually I got acquainted with Clifford Grobstein who was an eminent developmental biologist in the biology department at Stanford. This was just the beginning of the great days of Stanford. Arthur Kornberg and Paul Berg¹ and others had just arrived [1959]. There were very fine groups in Biology, Biochemistry, and also in Chemistry. So Stanford in ten years had become a super place. I decided to take a sabbatical leave [1962-1963] from Illinois to do science with Grobstein at Stanford.

¹See the oral histories with Arthur Kornberg, M.D., and Paul Berg, Ph.D., in the Program in the History of Biological Sciences and Biotechnology Series, Regional Oral History Office, University of California, Berkeley. Hereafter The Bancroft Library Series.

Guggenheim Fellow, Stanford University, 1962-1963

Rutter: Grobstein and collaborators had studied two systems: the salivary gland and the pancreas. We, in the end, decided to work on the pancreas for the reason that the proteins which it produces were very well known and biologically important. The pancreas produces prodigious amounts of the digestive enzymes, insulin in the islets of Langerhans, glucagon, somatostatin, and pancreatic polypeptide. At that time, nothing was known about the details by which the cells were determined to produce those molecules or anything about the embryological origin of the cells.

Grobstein and his colleagues had shown that the pancreas develops via an interaction between mesenchymal and epithelial cells, as a little bulb formed from a diverticulum developing at the joining of the stomach and intestine. In early development, mesenchymal cells form a cap over the epithelial cells of the diverticulum to form the initial bulb. The bulb then expands into the typical pancreatic acini connected via ducts to the pancreatic duct which delivers the exocrine enzyme into the gut.

I felt that it might be possible to define the differentiative process and the role of the mesenchyme. At that time I met Edward Penhoet, who was a senior undergraduate student, later my graduate student, and a co-founder of Chiron. Don Kennedy, who is now president of Stanford, and Charles Yanofsky, a distinguished molecular geneticist, were working next door. Norman Wessells, who eventually became the dean of humanities and sciences at Stanford, and is now provost at the University of Oregon, collaborated on the project. There were many excellent people in the immediate environment.

Penhoet became more or less my technician and collaborator on these experiments. We began to define stages when the expression of the enzymes was turned on in early developing pancreas, using very sensitive assays. This was about the first time one could measure the enzymes with great sensitivity and facility, which was necessary because the pancreases from early embryos were so small.

Hughes: What kind of pancreases were you using?

Rutter: Mice were the dominant animals. After one determined the pattern of expression of the enzymes during development, one could assay that aspect of differentiation and measure the effect of mesenchymal cells on epithelial cells in vitro.

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Rutter: The combination of mesenchymal cells and epithelial cells allows the epithelial cells to start developing into pancreatic structures. The questions were whether the signals are soluble compounds and whether these cells must physically contact each other. If not, then you could simply get an extract to make it work. I was able to show that an extract of mesenchymal cells could replace the mesenchymal cells. I think that is the first time that it was shown that soluble hormone-like factors involved are in differentiative transitions. I became fascinated with the mechanism of differentiation and about the process by which the cell-specific genes were turned on.

At that time, Illinois became a less attractive place to be. I was in the chemistry department, but my research no longer emphasized chemistry. I was more interested in genetics and in things that were more biological. Furthermore, I had grown up at Illinois; it was time to develop an independent career. I needed more space and a different kind of environment. So I decided to leave. I had a number of opportunities. I could go to Stanford for example, which was an attractive place. I also had the opportunity to be head of the department of biochemistry in several schools. However, I decided not to be a department head. I was interested in science.

Professor, Departments of Biochemistry and Genetics, University of Washington, 1965-1969

Rutter: Stanford was a terrifically attractive place at the time. I decided ultimately to go to the University of Washington where they had a great genetics department and an excellent biochemistry department that were in close proximity. I had freedom for research and was not required to do much teaching. The joint appointment with the genetics and biochemistry departments was very appealing to me, as was their relationship to the medical school.

Hughes: What did you plan to do there?

Rutter: I wanted to learn more genetics, which was possible. The genetics department emphasized simple eukaryotic systems, such as yeast.

Hughes: Who was there?

Rutter: The man in charge of the department was Herschel Roman. There were many young and vigorous people in the department; it was one of the avant-garde genetics departments in the world. Molecular

(mechanistic) genetics at that time was mostly done on bacteria. This department focused on yeast, which is a eukaryotic organism, that is, the cells contain a nucleus. I was really interested in the genetics of eukaryotic cells because revealing molecular mechanisms for a mammalian system such as the pancreas seemed impossible at that time.

So I continued to work on pancreatic gene expression and development, but I also began to focus on mechanisms of gene transcription; that is, making an RNA copy of the genes from DNA. This required an enzyme. It was obvious that one place to learn about specific gene expression from a mechanistic point of view was to start with the enzymes that transcribe the genes. The enzymes had to act specifically. Some kind of mechanism either intrinsic to the enzyme or involving factors bound to the enzyme or to the DNA had to signal, "transcribe this gene." Studying transcription was an approach to understanding specific gene expression.

Hughes: About which very little was known.

Rutter: About which virtually nothing was known. I was not interested in bacterial expression--in fact, a bacterial RNA polymerase had been described, but transcription in mammalian systems was largely unexplored.

I brought virtually all my lab from Illinois to Washington. We began to focus on the subject, as a new interest. The key person was a very talented young Indiana farm boy named Robert Roeder who is now a professor at the Rockefeller and a member of the National Academy [of Sciences]. Roeder started working on the RNA polymerase problem as a graduate student. We used a variety of systems, yeast and also sea urchins, which were in abundance up there, to be able to show the characteristics of the eukaryotic transcription system. Urchins have a very active transcription system during embryological development. There were excellent zoologists at Washington who studied phenomenology, but not molecular mechanisms, so our approaches complemented theirs.

We showed that in yeast, sea urchins, and also mammalian cells there are three distinct types of enzymes that transcribe the genes. Two of them are involved in making components ([RNA] polymerase I) that are associated with the translation mechanism; one makes ribosomal RNA, the other makes tRNA [transfer RNA] and other small RNAs that are involved in ribosomes or translational functions, or in various reactions of RNA processing (polymerase III). The other enzyme, which transcribed the genes involving proteins, was called polymerase II. We initially focused on

defining the structure of the enzymes and their role. The enzymes were very complicated multi-subunit molecules.

Studies we carried out in bacteria and in bacteriophages (bacterial viruses) showed that there were factors that could modify the specificity of the RNA polymerase and affect the transcription of certain genes. These were called sigma factors. There were also elements which bound eukaryotic RNA polymerase which might be analogous to sigma-type factors. The direction in which transcription would develop became sort of evident. The RNA polymerase problems became quite popular and the work on pancreatic development was going very well. We also carried out some interesting work on the structure and evolution of aldolases. I was having a great time learning lots of things.

II CHAIRMAN, DEPARTMENT OF BIOCHEMISTRY AND BIOPHYSICS,
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, 1968-1982

Dr. Rutter's Recruitment

Rutter: I had several interesting opportunities to be chairman of a department of biochemistry but I wasn't really interested. I loved living in Seattle. But then Holly [Lloyd Hollingsworth] Smith and Bert [J. Englebert] Dunphy paid me a visit. Holly was head of Medicine here. Bert Dunphy was head of Surgery. As I told you, my own interests at that time were oblique to medicine. I was interested primarily in the research I was doing; I was not interested in focusing on medical problems per se.

Over a period of a year and a half, I turned down the job at UCSF three or four times. Holly and Bert kept coming back.¹ Over several years, probably every good scientist in the United States had been asked to take that job; UCSF was trying desperately to become a first-class institution. Sooner or later all those asked turned it down. It was unpopular to do basic science in a medical school. The best science was really being practiced outside medical schools. The relationship between the clinical sciences and the basic sciences in medical schools generally was strained, perhaps because of consistently diverging interests. There was no easy way to address mechanistically and from a molecular point of view the most important problems of clinical medicine. Science had not progressed far enough to be able to ask sophisticated questions about complex physiology and clinical phenomena.

Hughes: This was a general problem, not one specific to UCSF?

¹ For example, see: Stuart C. Cullen to William J. Rutter, June 29, 1967. (William J. Rutter correspondence, MSS 94-54, Special Collections, UCSF Library, carton 1, folder: 28. Hereafter, Rutter correspondence.

Rutter: A general problem all over the world, for sure. Even departments in good places like Harvard were not doing well. Stanford at that time was one of the luminous schools. They had recently attracted very good basic scientists. However, it was widely believed that it would be extremely difficult to set up in a medical school a good graduate program that required real scientific resources.

On the other hand, the great thing about UCSF was that the clinical people were trying to improve the basic sciences. They were absolutely committed to bringing good science to UCSF, and furthermore they had many open positions to fill.

Hughes: Why do you think that Smith and Dunphy had this point of view?

Rutter: Because they were far-sighted. They understood, I think, that good clinical training required a mechanistic understanding which could be best obtained by practicing science in contiguity with clinical practice, that good clinical science required good basic science. Both had scientific interests which were to some extent compromised by the lack of availability of a basic scientific enterprise at UCSF. In trying to build an "academic" medical school, they had the foresight to understand the importance of building a fully integrated science program.

At that time, UCSF was unpopular and considered a mediocre institution. All my friends were saying, "Why leave a great place to go to a medical school?" But there were a number of strong attractions: first, the support at the school. [David M.] Papa Greenberg had retired in the early sixties; there was an acting chairman. Gradually, we consolidated the department to nearly twenty open positions. It was the only significant place in the United States where they had that many open positions. However, space was impossible. Despite the construction of two new research towers [Health Sciences East and West], the research labs were dispersed and not coordinated.

I realized this was a great opportunity. I'd said no for the last time, but by then they were about ready to recruit another person.¹ I had gotten all steamed about making a concerted onslaught on human biology. The best way was to bring together people with complementary talents and common interests.

Hughes: From various disciplines?

¹ For negotiations related to Rutter's acceptance, see: Rutter to Cullen, June 7, 1968, and Cullen to Rutter, June 11, 1968. (Rutter correspondence, carton 1, folder 28.)

Rutter: From various disciplines. It was also possible in the medical schools at that time for the chairman of the department to run the department as his own lab. It was very hierarchical. However, I saw it as the opportunity to make [UCSF] a strong institution by fostering scientific cooperation.

Hughes: In short, you saw this as an opportunity to build the department according to your own design.

Rutter: Yes, was given complete freedom. I believe I could have recruited twenty faculty who could have simply worked at my side on projects as an extension of my lab. However, I wanted to attract very good independent people from various disciplines who would work cooperatively on various facets of a major scientific problem. This was in fact quite different from the usual departments whose professors were chosen to represent distinct fields with little overall relationship, that is, one professor in carbohydrate chemistry, another in lipid chemistry, another in protein chemistry, another in metabolism, et cetera.

The longer I thought about it, the more excited I became about focusing on molecular mechanisms in higher organisms, especially humans. A combination of genetics, molecular genetics primarily, and biochemistry, was required to understand gene expression. Somehow we needed to develop strategies to deal experimentally with complex eukaryotic systems.

I called Holly to tell him I'd changed my mind. His first response was somewhat cool, believing it was simply some other strategy for continuing the negotiations without making a commitment.

Hughes: Why did they want you?

Rutter: Who knows? I think I was doing interesting new things, and was vigorous. I understand that Arthur Kornberg supported me.¹ They had seen a lot of people. Perhaps they had run out of prospects! But I did have some of the characteristics that were required to build a group in this kind of an environment. I was independent, energetic, and valued good science.

Hughes: It wasn't just that you were a good biochemist; they saw you as a way of moving into a different style of research?

¹ Arthur Kornberg to Dean Stuart C. Cullen, April 8, 1968. (Arthur Kornberg correspondence, Special Collections, Green Library, Stanford University, SC369, box 26, folder: 1968 (L-R).)

Rutter: I don't think that the clinical leaders had planned it this way. Above all they wanted a good department that worked on "hot" projects. Of course, if they were related to medical issues, so much the better.

Hughes: Nobody saw molecular biology as the wave of the future?

Rutter: One of the key professors in medicine, Isidore Edelman, who later became chairman of the Department of Biochemistry at Columbia, was one of the main proponents of good science here. Edelman was well aware of the great future of molecular genetics. In the Department of Microbiology were Leon Levintow, Mike Bishop, and Herbert Boyer. All were potentially excellent, but they were operating in a more or less sterile environment. Mike Bishop was working on reverse transcriptase at the time, Herb Boyer on restriction enzyme. Izzy Edelman worked on mechanisms of mineralocorticoid action. Izzy was very good friends with Gordon Tomkins.

Gordon was a remarkable guy. He was an M.D. and was tremendously bright and energetic and had a far-reaching scope. He was interested in mechanisms of gene expression and hormone actions. Gordon had gotten his medical training at Harvard and was recognized as one of the brightest and most interesting molecular endocrinologists.

Hughes: He was not yet here?

Rutter: He was at the NIH. In fact, he had been offered the chairmanship of biochemistry at UCSF some years before. He accepted and then at the last minute withdrew. Anyway, with Izzy's help I met Gordon and decided he would be a great colleague, and an ideal interface with the clinical departments.

Gordon became fascinated with the idea of helping to set up a eukaryotic biology program. We became good friends and so he decided to come to UCSF. He was my first recruit. He came as vice-chairman. I came in 1968 and he came in 1969.

Hughes: You accepted the position in 1968 but you didn't actually come until--

Rutter: I moved in 1969, but in fact I was down here about half time in 1968. I was excited about getting started.

Basic Science at UCSF

[Interview 2: March 10, 1992] ##

Before Dr. Rutter's Arrival

Hughes: Dr. Rutter, let's start with a little more background on the movement towards the basic biological sciences at UCSF.

Rutter: At first the basic sciences were housed at Berkeley, as you know. There was a question about whether one could ever mount significant basic science activities at the medical school. Eventually [1958], the basic science departments were moved here with Greenberg as the chair. There had been some distinguished individual scientists here.

In order to facilitate the development of research on the campus, the clinical departments and basic science groups sponsored the development [1958] of the Cardiovascular Research Institute [CVRI] with the notion that the institute itself could serve as a focus for research.¹ The head of this program was Julius Comroe, who brought a world-class program to UCSF. The CVRI really cut across departmental lines. Individuals held appointments in teaching departments but were also resident in an interdisciplinary institute that had cardiovascular research as its main interest. While this was good for the CVRI, it was not necessarily good for UCSF since strong independent programs did not develop.

Hughes: The Hooper Foundation [for Medical Research] had been established for many a year [1913]. That was also interdepartmental, was it not?

Rutter: Yes, the Hooper Foundation was established long ago.² It had a fine history but had a much narrower scope. It dealt primarily with infectious disease. Further, the Hooper Foundation itself was relatively small.

¹ For more on the creation and development of the CVRI, see: Cardiovascular Research Institute: The First Twenty-five Years, 1958-1983. University of California, San Francisco, n.d.

² For more on the Hooper, see the oral history with its first director, Karl F. Meyer. Regional Oral History Office, Bancroft Library, University of California, Berkeley, 1992.

There were several other institutes, but they made no or little impact on the science at UCSF, whereas the Cardiovascular Research Institute established a prominent theme: biophysicists, biochemists, physiologists, and clinical people, focusing on cardiovascular disease. This was a major internationally revered institute.

However, it wasn't in the long-term interests of the school to have its research dominated by the CVRI. A premiere school needed strong research in various departments. The preclinical departments at UCSF did have research programs, of course. But they were not distinguished and not integrated in a way to be synergetic so as to significantly enhance the reputation of the school as a center of excellent research.

For example, the biochemistry department was headed by Greenberg who established a program in protein chemistry with his colleague, [Harold] Tarver, within the classical theme that was common in biochemistry in the decades before 1960. The department was focused on enzyme chemistry, protein chemistry, and metabolism. Greenberg was a significant figure, a good man, but not a true luminary.

Recognizing the Need for a Molecular Approach

Rutter: The clinical departments became concerned that they needed someone that could catalyze research on a broader scale, research which was much more topical, perhaps relevant to medicine. They wanted to tap into the exciting lines of research which were emanating from more recent activities in molecular genetics. The issues of transcription and translation of proteins, and the dynamics of handling the major macromolecular entities which exist within cells, ones which were related in many respects to genetic and metabolic diseases, were of great interest to the clinical community. Interests in the cell surface and transport of molecules into and out of the cell also became very important at that time.

Hughes: More so than some of the other preclinical sciences such as physiology?

Rutter: Yes, indeed. Beginning in the late fifties and early sixties, the dominant interest of biological science was DNA and RNA, the establishment of the means by which genetics influenced cell function. This was fundamental to understanding everything else. There was a tremendous feeling of excitement about what those new

areas of science could contribute to an understanding of biology and pathology, and eventually clinical situations.

One of the hottest subjects in clinical medicine was the understanding of genetic diseases. Holly Smith was interested in that subject himself and had taken a sabbatical to study it. There was a sense of urgency within the Department of Medicine, which was clearly the strongest department here, as well as in Surgery, to establish a solid scientific organization here. Both Bert Dunphy and Holly Smith had come from Harvard and were committed to setting up another premiere center here on the West Coast. They saw basic science development as an urgent necessity if the school was to become a major academic center.

The Department of Biochemistry and Biophysics

Impediments to Recruiting a Chairman

Rutter: The key department in all this was Biochemistry because most of the methods emanated from molecularly oriented research. Physiology at that time was a field in which many of the important studies were pharmacological and were too complex to be resolved truly at the molecular level. On the other hand, physiologists had traditionally dealt with matters of importance to clinical medicine. Julius Comroe was a physiologist. The Cardiovascular Research Institute was primarily a physiologically oriented research institute. But Comroe was also a broad-gauged scientist, and brought in all the other modern technologies as well.

Hughes: Why then, with all this opportunity, did so many people turn down the chairmanship of Biochemistry?

Rutter: I mentioned to you last time that the best science was not being done in medical schools anywhere in the United States, with the exception of Stanford where Arthur Kornberg had established a superb department.¹ Harvard Medical School was also outstanding. Of course, UCSF did not wish to be outdone by Stanford. But many people looked at these drab old buildings and the strong orientation to clinical practice here as a barrier, and found the

¹ For descriptions of the organization and development of the Department of Biochemistry at Stanford, see the oral histories with Arthur Kornberg, M.D., and Paul Berg, Ph.D., in The Bancroft Library Series.

possibility of developing a first-rate scientific program rather daunting. In addition, in comparison to Berkeley, UCSF was severely disadvantaged. The scientists at Berkeley looked down on UCSF. Good scientists would ask themselves, why not go to Berkeley? There was no real graduate student program at UCSF. There was not a broad enough scientific base at the level of mathematics, chemistry, etc., to form a strong base for a distinguished scientific program.

Hughes: [The University of California at] Berkeley didn't count?

Rutter: To outsiders, Berkeley seemed too far away to directly contribute to UCSF. Traditionally, the insiders at UCSF relied on Berkeley, which in my view was a mistake because then UCSF became essentially an adjunct to Berkeley. Berkeley was very strong [in the basic sciences], and first class students didn't come here. If they were very good, why shouldn't they go to Berkeley? One had to establish a program which offered something that Berkeley didn't offer. This was a major problem because a scientific program had to be mounted on a fairly broad scale. It couldn't be done by the recruitment of a single group or two groups.

This fact was disturbing to me. My interest was research. I had an interest in graduate education, but I didn't want to spend my life building the system for graduate education when I had the alternative to spend my life doing something more directly related to the production of research information.

Hughes: Did it worry you that as chairman you were going to have to spend a lot more time on administrative duties? Before, as I gathered from your quick overview, you had the luxury of spending most of your time on science.

Rutter: That's the reason that I turned this job down several times. I didn't want to spend my time as an administrator. I was captivated with what I was doing. I assure you that being an administrator wasn't the reason I came here. In the end it became an issue of whether the opportunity was great enough to make a serious administrative responsibility palatable. Maybe we were a little bit naive, too. The enthusiasm for the program we envisioned was large enough that we were optimistic about solving some of the other issues, maybe more optimistic than we had any right to be.

Opportunities to Develop the Department

Hughes: What opportunities did you see? You mentioned the open positions, which of course were a big plus, but what else was there?

Rutter: There were a number of very good individuals. I mentioned Comroe. I saw the Cardiovascular Institute as being rather self-contained. It turned out to be that way, noninteractive in many respects. They weren't interested in helping the department because they were intensively involved with their own enterprise. To some extent, the activities and continued growth of the CVRI occurred to the detriment of the departments. These activities were competitive to some extent. Julius was much more powerful than any department chairman because of the budget he had and the position he occupied at the school. On the other hand, the departments knew that all of their interests weren't satisfied by Julius Comroe. There was a balance of interests and goals.

In the Department of Microbiology, Leon Levintow had come from the NIH, and was largely responsible for bringing talented molecularly oriented people into the department. As I mentioned, foremost there was Michael Bishop, an extraordinary individual, obviously very intelligent and doing excellent work. Herbert Boyer was also there. But at that time his program was not distinguished.

Hughes: Were these names that you were familiar with at the time, or only in retrospect?

Rutter: They weren't recognized scientists at the national level.

Hughes: Had you even pinpointed their existence?

Rutter: No. Only by coming down, did I recognize them as talented individuals who had vigorous programs and could be relied upon.

Hughes: So you had assessed the situation sufficiently to pick out individuals that you thought were up and coming and might even help your effort?

Rutter: Indeed. Leon, Mike, and Herbert were significant even though they weren't in the department. On the other hand, we had other individuals on the faculty who obviously were less attractive. The Department of Biochemistry was filled with people who were either difficult individuals, or they were outliers, that is, with insular laboratories devoted solely to the interests of the professor. They weren't building a cohesive interactive program. The department was fraught with bickering.

Hughes: What did you do about that?

Rutter: Izzy Edelman in the Department of Medicine, I think more than any individual at UCSF at the time, had a vision of quality science which was more practical than that of the heads of the departments, more dynamic in the sense he wanted to practice it, more global in the sense that he had a very broad interest in science at the detail level. Izzy was a very fine human being, supportive of individuals, a sane voice in a confused environment. He was a very important factor in supporting our activities. Many of the others in the biochemistry department didn't like him; in fact, they were antagonistic, very much antagonistic, toward Isidore Edelman.

Hughes: Why?

Rutter: I can't give all the reasons why. But they thought he wasn't a "real" biochemist; his credentials weren't the same as theirs.

Hughes: It wasn't that he was trying to lead their science in a different direction?

Rutter: I suspect Izzy was a key person in my recruitment. I would think that people in clinical medicine listened to Izzy. Others in the Department of Biochemistry might have chosen another individual.

What had happened over the years is that the number of positions in the department had increased. At one time it was thought that there should be a Department of Genetics, so the school invested the positions allocated to the Department of Genetics in the Department of Biochemistry and Biophysics. So the aggregate number was large enough to be the true beginning of a major department.

Hughes: Was it part of the arrangement when you arrived that the Department of Biochemistry would expand to include biophysics?

Rutter: Yes.¹ Dr. Greenberg had retired in 1963, if I remember correctly. Between that time and the time I came, the department had changed and more positions were added to it. We negotiated a mission that included biochemistry, biophysics, genetics, modern biology.

¹ See: Rutter to Dean Stuart Cullen, October, 1968; University of California Medical Center: Announcement, November 25, 1968. (School of Medicine. Dean. AR 90-56, Special Collections, UCSF Library, carton 1, folder: 19.)

Previously Appointed Faculty Members

Rutter: Several major groups were in the department. Manuel Morales, for example, was a well-known scientist who was also a member of the Cardiovascular Research Institute. He had a big laboratory and had, I would say, a special personal view about what Biochemistry should become.

Hughes: A special view that didn't coincide with yours?

Rutter: It wasn't coherent with the view that we would go into molecular genetics, the modern biology that we were espousing at the time. He was interested in more classical physical and protein chemistry, which obviously had its appeal as well. But we couldn't be powerful in every field. There were several professors, Frank Yang and Leonard Pelter, that either interacted with his lab or were part of his lab, so they acted as a functional unit with a singular point of view. In addition, there were also Tom Singer and Edna Kearney who were over at the Veterans Administration Hospital at Fort Miley, and who were classical biochemists interested in flavin biochemistry. They were strong but very difficult individuals. Ernest Kuhn had a joint appointment in Pharmaceutical Chemistry. He was also a difficult personality. Then there were other professors in the department: one was Richard Fineberg, a student of Papa Greenberg's, a very fine gentleman but not dynamic and not a tremendously good researcher. There was Dr. Edward L. Duggan who later committed suicide [1968]. One of the newer appointees was John Ofengand, who was Paul Berg's (Stanford) student, who was working on t[ransfer]RNA structure and function. Finally, there was Elizabeth Roboz-Einstein, a very interesting and dynamic woman, and the wife of Albert Einstein's son. She was also a faculty member at Berkeley.

I had known Tom Singer and Edna and also Ernest Kuhn from postdoc days at the University of Wisconsin. The possibility that I would ever meet these characters again, especially in the same department, seemed remote, and was an interesting twist of fate. We had to work with a group of strong-willed individuals, each with his or her own singular view about what should be done with the department and what their role should be in the future.

Hughes: How did you deal with that?

Rutter: I recounted to you how we decided to bring in Gordon Tomkins as head of a major research group and vice chairman. We wanted to establish a central research theme around human genetics. Our general strategy was over time to develop a more supportive and

interactive group around this general theme. That's what Gordon and I proceeded to do with some difficulty. We had many rancorous department meetings, but gradually things changed.

The great thing about Gordon as a colleague, besides his imagination, was his ebullient spirit, a tremendous sense of humor--a fantastic colleague. Gordon was a clinician, an M.D. by training, and he was known and respected by the clinical groups, so he was tremendously effective as an interface with the clinical community. He was also a charming person and remarkable lecturer --people liked to hear him talk. He also had a big lab. So it was infectious--my lab and his lab arrived here, and that started things. Forty new people began to change the environment.

Hiring New Faculty Members

Rutter: Then we began hiring key individuals one after another.

Hughes: Who were some of them?

Rutter: One of them was Howard Goodman. Another was James Spudich.

Hughes: Are you moving chronologically?

Rutter: Pretty much chronologically--Harvey Eisen, Reg[is] Kelly, Robert Stroud, Robert Fletterick.

Hughes: Always looking for people on your mission.

Rutter: Always looking for people who were interested in the molecular details of genetic expression, or macromolecular chemistry studied in a new way--new biology in a sense. This could be hormone action studied at the level of genetic expression. It could be genetic expression itself. It could be the technology associated with molecular genetics and so on. Each one came from a slightly different field but all had a common interest in new technology and new programs. We began developing an intensively interactive culture. We got together as a group to talk science. We developed an active seminar program.

Negotiating for Contiguous Space

Rutter: At that time, a big issue was contiguity of space. Prior to my coming, the department was dispersed. In order to develop our program, I negotiated for contiguous space.¹ I insisted that we have contiguous space because of the cooperative programs we wanted to build.

Hughes: This was a qualification for accepting the job?

Rutter: Yes. It would have been very difficult to establish a coherent department without having contiguous space. The other activities in the school were too heterogenous in direction and in quality.

Hughes: Did you make any other stipulations?

Rutter: Oh yes.² Of course, we secured the positions.

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Rutter: We had a budget, which I negotiated with the dean on an enterprise basis.³ The base budget came from the school and presumably from the state. Anything we got from other sources we could use. So we had a flexible approach to recruiting people and to supporting their programs.

Hughes: That was not the typical arrangement, here anyway?

Rutter: It was not a typical arrangement in the basic science departments in the United States to my knowledge. I thought the administration was very farsighted. It wasn't unlike the situation which existed in clinical departments, which had revenues from their group practices. But basic science departments did not. Hence, negotiating with the dean on every matter would have greatly restricted our ability to make appointments and to develop programs.

¹ See: Rutter to Cullen, June 7, 1968. (Rutter correspondence, carton 1, folder: WJR on chairmanship.)

² Ibid.

³ Ibid.

Faculty Recruitment

Rutter: We had enough flexibility that it was possible to tailor the appointment to the needs of the individual. That helped us immensely to regulate appointments. In addition, we brought in some great people from the outside as visiting professors or prospective long-term mentors. One of the key ones was Fritz Lipmann, the Nobel Prize winner, who was one of the great biochemical scientists. He was at Rockefeller Institute. We persuaded him to come here for six months at a time. We hoped he might move from the Rockefeller to San Francisco. Although he didn't move, he spread the word that this was a pretty good place to be.

Over time we were able to recruit very good people. It was important not to accept anybody who wasn't outstanding. Secondly, we brought scientists broadly recognized as outstanding, to participate in the development of the school.

Hughes: Were you the only one recruiting?

Rutter: No, Gordon and I worked together. We would always talk to each other and take suggestions from lots of people. A lot of my time was spent in getting to know the best young people.

Hughes: In Dr. [Leslie] Bennett's oral history, he says that one of the bones of contention was the discrepancy in salary between the clinical and the nonclinical faculty.¹

Rutter: It was a bone of contention to some extent; salary discrepancies are always an issue. But our fiscal flexibility allowed us to raise the salaries modestly, of course not anything like clinical salaries. We also had to compete with basic scientists in clinical departments that were paid near-clinical science salaries. This was a difficult situation.

But we didn't recruit people because they wanted to make more money than anybody else. We attracted people who really wanted to do good science and be recognized internationally for their work. In the end, our main competition was not the clinicians' salaries. Our main competition was the salaries that other institutions would provide for similar positions. So we put

¹ Conversations with Dr. Leslie Latty Bennett: The Research Tradition at UCSF. UCSF Oral History Program, Department of the History of Health Sciences, UCSF, 1992.

our money into building a good environment and into giving our faculty enough salary and flexibility to conduct their lives according to their personal goals. Thank heavens, the prices of houses in San Francisco were acceptable during that period of time.

[Interview 3: March 30, 1992] ##

Hughes: Did the administration's emphasis on the Department of Biochemistry cause resentment in the other departments, particularly the basic science departments?

Rutter: Of course. Other departments had successful but not outstanding programs because they had a limited amount of research. The Cardiovascular Research Institute was the major research group. Some of the other departments were anchored in the past. The strongest department was Physiology because Physiology was related to the Cardiovascular Research Institute.

The Department of Microbiology, with Ernie Jawetz, was focused on medical microbiology. There were four bright and relatively new additions, Michael Bishop, Herbert Boyer,¹ Leon Levintow, and Warren Levinson. Those people had been recruited primarily by Leon Levintow. They formed a nucleus of modern approaches to either molecular genetics or to virology. That segment of the department was eager to interact with Biochemistry. But I think that Ernie Jawetz, head of Microbiology, and Fran [William Francis] Ganong, head of Physiology, were not so positively oriented to the new biochemistry and biophysics.

Pharmacology was a classic pharmacology department. The clinical departments were not so happy about Pharmacology, although it had an affable chairman, Ernie Way. Pharmaceutical Chemistry in the School of Pharmacy also had a biochemistry group. It was more oriented to theoretical approaches and to chemistry per se. Thus they complemented our program. To some extent, every single one of those departments felt that we had obtained a disproportionate share of resources, that the dean was paying a lot of attention to us, and he was.

¹ An oral history in this series is in progress with Herbert Boyer. See the oral history with Herbert Boyer in the UCSF Biotechnology Series.

Policy Regarding Joint Appointments

Rutter: As we went forward, many people wanted joint appointments. In the University of California system that meant they could participate in the decision-making of the department. We gave them only reluctantly.

Hughes: Why?

Rutter: Without a common philosophy and objectives, it would have been impossible for us to act. All the joint appointments could vote in the department; we had to more or less keep control.

Hughes: But you had some.

Rutter: Yes, we did. Some were a result of past agreements, which were very difficult to break, for example, with Ernest Kuhn and Tom Singer. We gave appointments when we thought it was crucial for the development of some function of the school, and most of the time with the understanding that the individuals would have no say in departmental governance, and would not be housed in the department, nor have any kind of real call on its functions. They were joint appointments in the sense that individuals could acknowledge their affiliation in various publications.

Most of the time joint appointments were a necessity for recruitment. For example, we gave one to Finn Siteri of Obstetrics and Gynecology in the Institute with Bob Jaffe. That was contentious because Finn wasn't a person we would have directly recruited to the department. Nevertheless, we tried to accommodate the needs of the clinical departments when it was considered very important.

Hughes: Why was that particular appointment considered important?

Rutter: We wanted to recruit Bob Jaffe, who was an outstanding person in the field; this was a condition of his coming. We were unsuccessful in changing his mind.

Hughes: Were there any appointments that were based on research collaboration?

Rutter: Research collaborations occurred between the departments, but independent of academic appointments. We did give appointments to Michael Bishop, Herb Boyer, and Leon Levintow. Warren Levinson was also a member of the group, but I don't think he had an appointment. He was more inclined to be a teacher, but he did have a limited research program.

When Fran Ganong began to hire people in neurobiology, we helped influence that by participating directly in recruitment. People recruited in this manner usually received joint appointments because then it was easier to recruit them. This became the style. If we were involved in a recruitment, we would give a joint appointment; if we were not involved, we wouldn't. This policy helped to leverage our own status and visibility and spread quality more broadly than our own numbers. For example, we helped to recruit an excellent group of neurobiologists to the Department of Physiology under Zach Hall and Lou[is] Reichert. Zach Hall is now head of Physiology.¹ Eventually we established a very good relationship.

The same thing happened with Pharmacology: several key appointments were made, using in part their relationship with Biochemistry. We also established a good relationship with Pharmaceutical Chemistry, and they began recruiting people who were compatible with our group. The same was true in Anatomy. The head of Anatomy, Pete Ralston, was and is a very affable person. He always tried to recruit people who would be compatible with and respected by our group. We always interviewed their candidates. Gail Martin was perhaps the most closely allied individual.

So we transformed ourselves from a position of being somewhat antagonistic towards the other groups to a position of helping others to develop their programs in order to develop a more distinguished scientific community.

A Molecular Approach

Hughes: Was the common denominator a molecular approach?

Rutter: Not always, but mostly molecular and genetic. Even cell biology had an interest in molecular mechanisms involving DNA, RNA, and proteins. Many were interested in the regulation of higher cells by hormones, especially where the hormones have an effect on the expression of the genetic repertoire of the cells. That fundamental system was involved in nearly all the phenomena that many in the business were studying, so everybody was excited about incorporating one or another aspect of this program in their own programs.

¹ As of 1997, Zach Hall was director of the National Institute of Neurological Diseases and Blindness, NIH. As of 1998, he has returned to UCSF.

Hughes: You were encouraging interests that had already been expressed by these different groups?

Rutter: The discovery of DNA [structure] after all had occurred fifteen years before.

Hughes: I meant specifically on this campus, which as you described it, had been a somewhat old-fashioned place. You didn't inspire these interests; these interests were already present, but not developed.

Rutter: With the exception of these few people in Microbiology--and their strategy of doing research was totally different--individuals who were interested in a molecular approach frequently did not work directly on research in this area, which was fast moving and used different technology.

At first we were interlopers, but once we developed a critical mass, and our programs began to be recognized, the situation rapidly changed within a period of three or four years to one where we could help other people get on with their programs, but more oriented to molecular biology.

Hughes: To put it in a nutshell, you and the department were a catalyst.

Rutter: That's true.

The Basic Science Departments: Collective Action

Rutter: The department itself certainly acted as a catalyst at the research level. We also started for the first time to have a meeting of the department chairmen in the basic sciences. This group began acting collectively on the best interests of the school.

Hughes: Very soon after you arrived?

Rutter: Not very soon, two or three years perhaps. We began to discuss common problems; UCSF departments began acting as a unit.

Prior to that time, we had only one forum in which to interact, the [School of Medicine] executive committee, on which only a limited number of chairmen sat. I was always on the executive committee, Fran Ganong most of the time, and there was usually one other basic science chairman. Faculty meetings were never a forum for discussing high-level issues.

Hughes: Why was that?

Rutter: Because it was too mixed an audience. Change always involves some controversy and compromises. It's probably the most dangerous thing to start talking broadly about the various options before the key individuals have largely agreed on a path. The issues had to be quite carefully presented and sold.

Hughes: You were doing that?

Rutter: That was my job, basically. We had a very strong support group: the head of Medicine, Holly Smith; the head of Surgery, Bert Dunphy, who were the people that recruited me. Also the head of Pediatrics, Mel[vin M.] Grumbach, who was a farsighted person, and a number of other clinical groups in the school supported our program, as well as the dean, Julie [Julius R.] Krevans and Phil[ip R.] Lee, the chancellor. It was a complicated situation and there were many currents.

Consolidating the Department

Rutter: For example, shortly after I got here, the dean of [the School of] Pharmacy tried to take back some space. The dean of [the School of] Medicine, Julie Krevans, also tried to renege on some space.

Hughes: This was space that had been promised to you?

Rutter: Yes. I found it very easy to persuade the dean of Pharmacy that it was to our mutual advantage for us to keep the space, but the dean of Medicine was more serious. We had to be pretty firm on this matter.

Hughes: How did it work out?

Rutter: We kept the space.

Hughes: [laughter] But how?

Rutter: We gave him the choice of keeping his commitments on space or we would leave.

Hughes: That's pretty clear, isn't it?

Rutter: On rare occasions, it was absolutely necessary to be resolute. Because of countervailing forces, it would have been very easy to lose our strength and position in order to solve the major space

issues of the school. In the guise of good fellowship, we could have lost the entire program.

Hughes: Did you lose good fellowship over the ultimatum with Dr. Krevans?

Rutter: I don't think so. But for sure I was a strong-willed and contentious person, no doubt about that.

Hughes: Was that the first strong stand you had to take?

Rutter: For sure, not the first. The first strong stand involved encouraging people in the department who were second-rate to leave UCSF. You can imagine that is never an easy thing because people are always trying hard to succeed and are usually reasonably good scientists and also fine people. But they didn't fit my plans for the department. I remember we got unsolicited letters of support from a distinguished professor at Stanford, who very strongly supported one of his former postdocs who was a faculty member here. We had nevertheless made the decision to encourage him to leave.

There were people who were not only trying to keep their positions but also to gain strength. Several in the department were more or less hangers-on, using needed space without helping our program or developing a distinguished program [of their own]. The toughest job I had was, in as humane a way as possible, to get these people to seek other jobs. I gave them a lot of flexibility; I tried to get them good jobs, to the extent I could.

Hughes: You came with the idea that the entire department would be working on your program?

Rutter: No, not on my program. We had plenty of flexibility in our [departmental] program as long as it focused on some aspect of human molecular genetics and was potentially a first-rate scientific program likely to produce unique new information.

Hughes: Many of the people who were here when you arrived were not working in molecular genetics.

Rutter: Yes. We had some verbal battles with several of the major groups, Manuel Morales and his group in the Cardiovascular Research Institute, for example. I'm not sure whether Manuel called me "The General," but he used to call Gordon Tomkins my "lieutenant". Manuel would bring his entourage to departmental meetings and insult Gordon terribly. Manuel wanted to use department resources to further biophysics; his interests were incompatible with ours.

Hughes: Even though you wanted to have biophysicists in the department.

Rutter: Yes, [but] we needed good science devoted to structure, not just physical measurements. In later years, Manuel supported our program. He borrowed biological reagents and technology from my lab. But in the early years, he was always trying to get his own people appointed to faculty positions, individuals who were being (and should have been) carried on his research grants. A frequently used strategy in those days was, whenever possible, to use state-supported FTEs [full-time equivalent positions] for individuals working on a faculty program. This leveraged whatever grant activity the professor had. This was absolutely the worst use of university resources because those individuals had a hard time, even in relatively good times, getting an independently funded program. It didn't provide real strengths to the school. Overall, the quality of the department would have been lowered.

Because the drive by senior professors for this kind of activity was so high, and the rewards to these people in terms of their own programs were so great, it became a real issue in this and other schools. I was always grateful that David Greenberg, "Papa Greenberg" as he was called, never played politics within the department. He supported my position, or at least he didn't interfere. I gave him an office. For years and years, until his late eighties, he came to seminars. Then his colleague, Harold Tarver, worked for several years, and he occupied some small labs in another part of the institution.

[Biomathematics and Crystallography¹ ##

Rutter: The department was kind of a microcosm of science. Its functions were much broader than an ordinary department. Our interests in biochemistry and biophysics could not be restricted to molecular genetics alone. I believed we had to study structure-function of macromolecules. Understanding structure would contribute greatly to understanding function. This was not a view widely held in departments focused on molecular genetics.

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Rutter: The biomathematics program of the department as an example of how the medical center was willing to coalesce biochemistry and biophysics and related sciences to include essentially all of the scientific elements that weren't large enough to become separate

¹ This section is an amalgam of discussions on March 30 and April 18, 1992.

departments. Biomathematics itself was set up before I arrived in 1969 to serve the statistical needs of medical and other science departments because, naturally, some of the people hadn't had sufficient mathematical and statistical training and needed an infusion of mathematical know-how. In addition, the school had a feeling that they should have some fundamental mathematics so that this discipline would be represented on this campus.

There was a small group, just two professors, who formed the biomathematics group in our department. One of them, Hugo Martinez, eventually developed computer programs that were very useful to the individuals interested in nucleic acid sequencing and structure. Hugo developed computer programs not only to record sequence information but to predict secondary structure, to translate the sequences into structure so you could make comparisons at the amino acid level, to identify introns, to compare known sequence at the nucleotide and amino acid levels in the database, and so on.

Hughes: Was he somebody you brought in?

Rutter: No, he was there.

Hughes: In the Department of Biochemistry?

Rutter: At first, it was a separate group in biomathematics. Later, the biomathematicians were brought into the department. Afterwards, we tried to interest them in the main themes of the department. Hugo Martinez became very interested, got himself a nice computer for those days, and helped a lot. In fact, at the time that we were doing structures, we had one of the few computer-based systems to deal with these issues. It was really very helpful.

Hughes: This is the early seventies?

Rutter: Early seventies.

Hughes: It was unusual to have biomathematicians in a department of biochemistry?

Rutter: Maybe even unique. It was one of the advantages that UCSF held over other places. Larger institutions would have a separate department of mathematics with its own intrinsic interests. It might be possible to get one of those people interested in your programs but it wouldn't be as easy to facilitate that kind of interaction as it was in our own department. And then there was always a way to motivate them to work on your programs: one could find some money to help them buy a computer or recruit some student or try to do this or that with them.

Hughes: Which you did.

Rutter: Which we tried to do. Yes, indeed.

Hughes: You realized that the biomathematical approach was going to be one of the necessary tools to unravel cell mechanisms?

Rutter: Yes, indeed. And also the structural approach.

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Hughes: Was it happenstance that the biomathematicians were in the department when you arrived?

Rutter: They weren't in the department when I looked at the job. They were not assigned to any particular department. We negotiated to have them attached to the department.

Hughes: According to an annual report of the department, they were initially brought in on a temporary basis.¹

Rutter: That's right.

Hughes: Why?

Rutter: Because at first it wasn't obvious even to me that the department was the best home for them. We thought we would try it out. It was my intention to incorporate some aspects of their activities into data storage and retrieval, modeling, and the development of sophisticated physical approaches to structure. Hugo Martinez played a very important role in the latter. Relatively early on, we began to recruit x-ray crystallographers. We didn't hire one x-ray crystallographer; we hired two because we needed to have a critical mass and to make a significant commitment to this discipline. Two of them are still here, Bob Stroud and Bob Fletterick. They have since been joined by David Agaard.

We had others who were oriented toward structure. In the so-called Morales group working in the CVRI, Frank Yang worked on light scattering with a famous guy at Harvard called Moffitt. They developed the Moffitt-Yang equation which describes the fundamental role of light scattering in structure determination. There were various other indirect ways to establish structure, but they never gave precise information. Since they didn't provide

¹ University of California San Francisco, Department of Biochemistry and Biophysics, Annual Report 1970 [n.p.]. Copies of annual reports are located in the library of the Department of Biochemistry.

atomic detail, but simply an aspect of form, they were of little interest to me. We were more interested in specific structures, so we invested in programs that revealed the precise interactions of atoms.

Hughes: Did you have any trouble justifying two?

Rutter: We didn't have to justify two to anybody. [laughter] One of the nice parts about my position was that I had considerable freedom provided the quality of the [structure] work was good and the core group in the department supported my program.

Although we had department meetings to discuss all major issues, I never called for a vote. We discussed matters and then we made decisions by consensus. I usually dealt one-to-one with the people who had strong opinions, in order to try to come to a consensus without requiring a vote. In building a department, it was very important to have the continuing support of the faculty and the dean, but also to have freedom. We had no specific recruiting committees. I considered it one of my prime responsibilities as chairman.

Recruitment

Rutter: What was great about the recruiting process at UCSF is that everybody wanted to develop an outstanding department. Many people in the school suggested possible faculty. We always listened but we were very selective. We didn't try to hire too rapidly. We waited for unusual individuals. Many were hesitant to come during the early phase of building the department. But we had space and resources and the freedom, to some extent, to make arrangements consistent with the needs of the people who were involved. One of the great disadvantages of the current situation at UCSF is that procedures have become so codified that either you deliberately bypass the rules or you can't compete with the offers from schools that have a good deal more freedom and available resource.

In our situation, goodwill, cooperative attitude, and high scientific goals, in short, the excellent environment, were the attraction. When people became identified with our vision, it was easy to work out something that was acceptable for them. We paid a lot of attention to recruiting. Gordon was a fabulous person, tremendously engaging, a gifted intellectual with broad scientific interests. We both traveled a great deal and identified many possible colleagues. Then I would spend a great deal of time

trying to figure out whether a candidate would be an outstanding scientist and colleague, not just whether his scientific talents and drives were outstanding but whether he or she had intrinsically good motives and high values.

Hughes: How did you determine that?

Rutter: By conversation with the individual and others who knew him well.

We sought individuals who were not just technically competent but who understood how scientific understanding develops and had a strategic sense about their own careers, a sense of where they fit in science at a particular time, and how they could make a contribution to the field. I look for people who have a sense of mission and who are oriented to conceptualization and the technical aspects of problem solving. Strategic sense is a tremendously important aspect of a career.

Strategic Sense and "Taste" in Science

Hughes: How does a person develop strategy?

Rutter: I suppose it is taught to some degree by example, and some of it is intrinsic. I can't answer that question well.

I noticed early in my training that people who were making great contributions were strategists, in addition to being experimentalists. Most were also great competitors. So strategy didn't only involve planning an effective program, but also involved anticipating the competition and developing the most effective means of providing the most novel approaches to the key questions of the time.

There was a Nobel Prize winner named Fritz Lippman whom we brought to San Francisco from the Rockefeller for several months at a time over a period of several years. He was a truly unusual scientist. He was at the end of his career but still was a keen scientist. He was not very articulate in public. He would roll his eyes up and sometimes make confusing remarks about his science. Most people thought he was a dreamy, totally intuitive scientist. But that was far from the case. In fact, he had a razor-sharp mind and a crisp sense of strategy--one of the most interesting strategists that I have ever met. It was no accident whatsoever that he was successful in science.

Lippman was very competitive, although you'd never believe so by virtue of his demeanor. There were many great scientists in those days--it was the end of the first great tradition in biochemistry. Many of them showed that kind of behavior, for example, the famous [Hans A.] Krebs, of the Krebs cycle.

Krebs also became a friend of mine. He appeared to be a quite distant person but he was tremendously acute and engaging. In several meetings that we attended, we would speak in half sentences with much tacitly understood, really communicating by just a few words. This kind of special communication was quite humorous, or frustrating, to others. It was tremendously fun to interact with him because he was so strategic and so quick to discover the meaning of complex data. I sought and enjoyed people who had that kind of scientific versatility.

Hughes: Including postdocs and graduate students?

Rutter: Of course, it's not easy to communicate in that fashion with graduate students, because they don't have sufficient information. They have not yet developed what I call "taste". You can't have taste without having experienced a wide variety of foods. I think it is possible to have taste in science. When one knows enough science and has developed a philosophy, one can decide what issues are important from both a conceptual and a practical point of view. Once you've been in it long enough, you can decide what's important to you.

For me, taste requires discriminating which issues or approaches are of highest quality, most unusual or heuristic, and potentially revealing. In science there is a major difference between a true contributor and one who perhaps does good science, but on a limited level. Taste allows you to decide how to spend your time effectively. First of all, you must decide your time is worth something and, in that context, that the problem is worth solving--the best use of your time.

Hughes: Taste, then, involves more than science?

Rutter: Yes, it extends to all issues of quality. But as a scientist, when I use this term, I mean the elements of judgement that determine true value: novelty, importance, and the tactics employed in the prospective solution. Do you have the group that can solve it? How do you solve it most rapidly? Will the answer to the question change things? What kind of impact will it have?

Hughes: To do science tastefully, you have to be aware of different realms and how they interact. It isn't enough to be just a laboratory scientist.

Rutter: Exactly. You have to put the question in the context of the problems of the field and of society, in the broader context of the issues which need to be solved. It's not just impact on a certain scientific question; it's impact on how science affects society. What's appropriate under the circumstances? All those issues make the choice of a problem and the strategy of its resolution quite marvelous.

Hughes: Were you good at picking strategists? People with taste?

Rutter: I think so. We were pretty good at picking people who had a vision, an intense interest, a broad commitment, who were good at choosing areas that needed to be studied, and who seemed to be at the right place at the right time. This was always a main objective for us because we felt that to make our concept effective, we had to share technologies and do cooperative experiments.

The Department's Collaborative Approach

Rutter: This view was not usual in science, either in America or abroad. Of course people collaborated occasionally, but it was not the usual pattern. Most scientists wanted to set up an independent lab to focus on some subject and became totally competent to deal with that subject. In contrast, if one wished to attack broader issues, I believed that most of the answers would come from the interfaces, from combinations of disciplines. So collaboration should be the rule. That's the reason that we began to recruit multidisciplinary groups within the department. Each group, however, was interested in some aspect of the fundamental genetic macromolecules, nucleic acids and proteins.

We started a trend of scientific cooperation which was totally different from the standard practice of premier schools, like Harvard where the professors typically established self-contained laboratories. Our system in practice was exhilarating, infectious. People wanted to become involved because they could do good experiments, better experiments, more rapidly. The goal was to obtain new information in the most rapid and elegant way.

Hughes: Had you seen this cooperative approach in operation elsewhere?

Rutter: No, not really. But I started to think this way very early in my career as a postdoc at Wisconsin and in Sweden. When I was in Henry Lardy's lab at Wisconsin, I became interested in enzyme mechanisms. I predicted an enzyme-catalyzed exchange reaction,

which was an unusual concept. In order to investigate this, I had to measure deuterium incorporation into a substrate. We didn't have this methodology available, so I had to work cooperatively with someone else to do that experiment.

Then I decided to go to Sweden to employ a different methodology to solve this problem. When I got to Sweden, I found the methods weren't applicable for several reasons. I became involved in about ten different projects, mostly in collaboration with others in the lab. This way I learned more and produced more. I took advantage of the knowledge and expertise of the people around me, and I also gave them something that they didn't have.

After my sojourn in Sweden, I went to Marburg for three months because I'd met a German professor at a scientific meeting in Kiel. After talking, we decided to do some experiments together. It was just the best way; if you were interested in solving problems; cooperation seemed fundamental to success. There was always someone who had the best complementary idea or technology.

Gordon had very much the same attitude. He was a tremendously gregarious person and believed in doing things with other people. There was an intrinsic compatibility in our outlooks on good science. It was interactive science, which was different from the more structured approach of Manuel Morales, for example. He had multidisciplinary groups working for him, but they were all part of his team. They reported to him, so his ideas dominated. It wasn't important for me or for Gordon to have anybody report to us. It was our idea to get the best people you could get in each of the areas of significance. These individuals had independent programs, and then collaboration could occur at any level. It made sense to collaborate.

Hughes: So each of these subgroups was independent.

Rutter: Absolutely. There was no way that top-flight scientists would come to UCSF without a very strong independent program. We tried to pick people who had broad and compatible interests, who liked to collaborate, who were interested in the broader aspects of science, who were interested in cell biology.

Hughes: And indeed it worked out this way.

Rutter: It worked out this way. If you take a look at our department groups, you will see many, many collaborations. We succeeded as a group, as opposed to Berkeley, as opposed to Harvard, and, to some extent, as opposed to Stanford as well. Stanford had a superior

group in biochemistry; there are two Nobel prize winners there [Arthur Kornberg and Paul Berg] for example. They have absolutely superb people in that department. They interacted, worked tightly as a departmental group, but not to the same degree we did. They weren't as open within the Stanford medical complex. They didn't play a catalytic role [in the school of medicine].

Choh Hao Li and the Hormone Research Laboratory¹

Characteristics of the Laboratory

Rutter: One of the most antagonistic individuals was Choh Hao Li, who occupied this floor [the tenth floor of the Health Sciences Towers where the Hormone Research Institute is located]. Choh Hao Li was a powerful figure whose work on growth hormone and related molecules was internationally recognized. Furthermore, he was supported by well-known patrons of science, such as Mary Lasker.

Hughes: Why was he particularly antagonistic?

Rutter: He didn't want to participate in the scientific or educational program of the department. Nevertheless, he wanted the department and the school to continue to directly underwrite his science. He preferred to negotiate directly with the dean, not with me. So it was difficult to have a dialogue with him directly on any of the important issues.

Hughes: Was he used to running his own show?

Rutter: Oh yes. He was brought over here from Berkeley under some kind of special arrangement and had this entire floor, with the exception of a little laboratory that Reg Kelly now occupies and that I

¹ In 1956, the UC Regents established the Hormone Research Laboratory [HRL] as an organized research unit at UC Berkeley. However, Li, its director, dated its activities to 1952. In 1960, HRL became a unit of UC San Francisco, but did not move to UCSF until the Health Science Towers were completed in 1967. When Rutter succeeded Li as director in 1983, the name was changed to the Hormone Research Institute.

first moved into when I moved to San Francisco. It was a huge amount of space. Li was noninteractive with the department and in the life of the campus.

Hughes: He had never taught?

Rutter: I would not say never, but outside his own group and aside from giving some honorific seminars, I doubt very seriously that he ever participated in teaching. The Hormone Research Laboratory was a separate research unit, supported by the university. This structure isolated him from everything else.

He had a mixture of people of varying qualities. One of his people, [J.] Ramachandran, used to support our teaching program. He was quite a good protein chemist and endocrinologist, but his research and participation in department activities was strongly regulated by Choh Hao. Only years later, near his retirement [1982], did Choh Hao Li and I become conversant. We never had a true scientific exchange; he simply "lectured" me on his scientific contributions.

Hughes: Did you let him run his show?

Rutter: I had no direct control over Li, except formally I did control his FTE. As head of an independent research unit, he reported directly to the chancellor.

I didn't quarrel with anybody as long as we could get enough space and services. At that time, I had no quarrel with the deals that the other people had made in the past. I thought it best not to tilt with the strongest people in the school.

Li as a Personality

Hughes: What was Li like as a personality?

Rutter: He was a mandarin in every sense of the word, a sophisticated and very interesting person. He was also distant and arrogant in many respects. People in his laboratory were treated as part of his "family", much as you would have found in old Japan or Germany, where the professor is truly the Geheimrat, the honored leader, the head of the clan. He expected to be treated, and was treated, with great deference. He wanted to be supported and allowed to operate totally independently. It was an absolutely marvelous situation for Choh Hao Li.

Hughes: What did you think of his work?

Rutter: He was a good protein chemist, though he had made significant errors in the structure of human growth hormone, his major contribution. However, Li was not a broad-gauged scientist with great insights. In short, I didn't think he was as good as he was touted to be.

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Rutter: He was the kind of person that advertised that he was a candidate for a Nobel Prize. This was leaked to the newspapers at the time the prize was offered. His name was frequently mentioned in the press as one of the great scientists of the day. Of course part of this came from the school's publicity campaign, but certainly Li also fostered this image.

Hughes: Did he have any dealings with Herbert Evans when you knew him?

Rutter: He actually worked for Herbert Evans, but Herbert Evans wasn't around when I was here.

Hughes: Had he retired?

Rutter: He had retired; I think he was still alive.¹

Hughes: He was very much alive in the mid sixties when I was a student in histology. He used to peer down my microscope.

Rutter: Really! I always wanted to meet Herbert Evans, but I never had the pleasure. Of course, he was a major figure in the school. The school was oriented to physiology and endocrinology--his interests. His students and associates held powerful positions. In some ways UCSF was like the Max Planck Institute, with Herbert Evans as the ultimate Geheimrat.

Another organized research unit, the Cardiovascular Research Institute, was totally different and a countervailing force, the result of Julius Comroe's vision. The CVRI ultimately became the most important force in the school because directly or indirectly it controlled space and resources. People would be appointed in a department and also in the Cardiovascular Research Institute. To his credit, Julius Comroe put together programs around a powerful medical theme. It was recognized as a strong program nationwide

¹ Herbert McLean Evans, M.D., Sc.D., died in 1971. His papers are housed in the Bancroft Library, University of California, Berkeley.

and, I believe, influenced the NIH to adopt the program-project orientation.

Hughes: Isolation is not built into the structure of an organized research unit?

Rutter: No, not at all.

More on X-ray Crystallography

[Interview 4: April 19, 1992] ##

Rutter: I mentioned that we developed quite a significant x-ray crystallography group. This is a physical analysis which obviously deals with diffraction of x-rays. So one must deconvolute light diffracted by crystals collected at first as signals on film, and then afterwards by electronic means, and more recently deconvoluted by computers.

This was a highly mathematical game that also wasn't usually carried out in biochemistry departments because very few biochemistry departments had strong structure groups. Neither Stanford nor Berkeley had an x-ray crystallography group. There were x-ray crystallographers at Harvard but not in the Department of Biochemistry.

Genetics in the Department and at Berkeley

Rutter: The genetics group was an important addition to the department. Classical genetics could have been animal genetics, usually studied in mice; or human genetics, studied in populations or in individuals with obvious defects; or in Drosophila; or in microorganisms, usually bacteria or yeast. In all of these cases, classical programs were being oriented toward molecular approaches, that is, to understanding genetic mechanisms in terms of DNA sequence or protein sequence and in terms of the reactions catalyzed, and to using mutations to study processes like transcription and translation. All those things were happening. Of course they were central to understanding biology in the human.

Hughes: They were happening elsewhere but not at UCSF?

Rutter: They were not happening at UCSF in the late sixties and early seventies. The whole field was in transition, the structure of DNA having been discovered in the early fifties. In this early period, the majority of the studies focused on physiological medical genetics rather than mechanistic genetics. Luckily for us, when I arrived at UCSF, they hadn't recruited a genetics department so they agreed to put these positions in Biochemistry.

Hughes: But the positions had been created.

Rutter: They had been allocated some years before, I believe in the early 1960s.¹

Hughes: Do you know the story? Who was behind it?

Rutter: I really don't know the whole story. This occurred in the early sixties, so it must have been John Saunders who agreed to it. This was a time when the university was building its campuses and when they were developing the basic science groups at UCSF.

Hughes: So genetics would be a logical component.

Rutter: It would be a necessary component.

Hughes: What was happening at Berkeley?

Rutter: Berkeley had a very fine genetics department, a classical genetics department, but it was not a place where much molecular genetics was practiced. But they had people like Gunther Stent in molecular biology who was a leading molecular geneticist.

Hughes: Kurt Stern?

Rutter: Yes, indeed. He was a classical geneticist.

People who were interested in molecular genetics were primarily in the Virus Lab. The microbiology department was largely devoted to metabolic microbiology. The biochemistry department was a classical biochemistry group. So the Virus Lab was a logical place for this new focus.

Hughes: Was there ever a particular connection between the Virus Lab and the medical school?

¹ For information related to genetics at UCSF, see documents dated as early as 1961 in Special Collections, UCSF Library (School of Medicine, Dean. AR90-56, carton 10, folder: 207.)

Rutter: No, there was no significant connection and a quite distant connection between the medical school and Berkeley itself. Just at the time our department was beginning, Gunther, (who is a friend of mine, a very sophisticated intellect), pronounced that the golden age of molecular genetics was dead. [laughter] He wrote a book about it.¹ The basic thesis was that we know the fundamentals, so the rest is derivative.

Hughes: Meaning the double helix and all that?

Rutter: The basic structure of DNA, the coding rules, the specificity of the code, transfer RNAs as adaptors, how translation works (initiation factors and termination factors). So his point was there's not much to discover that adds conceptually to the story.

Hughes: Did you ever argue that point with him?

Rutter: Oh yes. We laughed about it.

Gunther's point was that in microbial systems, one could see the end game. Then he moved to neurobiology, started studying leeches, and became fascinated with simple neural systems. At that time, the great future was thought to be the mystery of the brain and other complex processes, moving "forward" from simple molecular genetics. His reaction was typical of many of the sophisticated scientists on the frontiers of molecular genetics at that time.

Many of them were physicists, like Don Glaser who won a Nobel Prize for the bubble chamber for detecting subnuclear particles, and Seymour Benzer. A group of tremendously talented individuals began seeking other fields because molecular genetics was more or less "finished." They did not realize that the secret to the analysis of these other fields would really come through molecular genetics. It had to come through some kind of molecular strategy, not through mere observations of neural systems.

In fairness to those talented individuals, they tried to develop simple systems that were subject to genetic analysis in some way. The fruit fly experiments of Seymour Benzer are illustrative of this approach. But nevertheless, at the end of the sixties or early seventies, there was a logical pause because of this huge, intense interest in microbial genetics. Interestingly, the end game is still to be accomplished: the complete sequencing of the E. coli genome, and relating the

¹ Gunther S. Stent. The Coming of the Golden Age: A View of the End of Progress. New York: Natural History Press, 1969.

genetics to the sequence and understanding all of the regulatory networks.

Hughes: But surely they must have thought about the mammalian cell the way you were doing?

Rutter: Everybody did, of course. I was specifically interested in developmental biology as well as genetics. In developmental biology meetings, general genetic mechanisms without any specificity were proposed for complex regulatory processes. Once you had a system to regulate the expression of the gene, then you must consider genes regulating genes. And then the question is how do you stop this regulatory network? These were theoretical, not actual, considerations of course.

I think it was broadly recognized that there were special regulatory systems operative in eukaryotic cells, but they were believed to be just several orders of magnitude more difficult to investigate and hence would be only a technical problem. So people moved in other directions.

Yeast, Drosophila, and Nematode Genetics

Rutter: There was at that time a general move from bacterial genetics, coli genetics, to eukaryotic genetics. One of the reasons I moved to the University of Washington was that they had a very fine genetics department, especially in yeast, a eukaryote. While this was a great system, by the time I came down here, I had become convinced that it was time to face the complexity and the challenges of other eukaryotic systems, including the mammalian cell.

Hughes: Was that a significant turning point when you moved to the mammalian cell?

Rutter: Yes, when we started the departmental genetics activities, we selected against bacterial geneticists and sought individuals who focused on yeast and Drosophila. For example, Ira Heřskowitz was both a yeast geneticist and phage geneticist. We felt these systems would provide understanding of higher cells.

Hughes: Which was your idea of the department's focus.

Rutter: Yes, exactly. This kind of thinking was going on in various places throughout the world. But I think in no other biochemistry department was there the focus on the range of scientific

approaches to the higher eukaryotic cell and eventually the human that there was here.

In the genetics division,¹ for example, we developed yeast, but as quickly as possible we also focused on Drosophila. Drosophila was attractive because of the immense genetic information already available, and, secondly, it's a complex enough organism so that one can begin to get molecular and structural information on complex processes. Yet it was simple enough to do both classical genetics and potentially molecular genetics. Today one sees that many mechanisms being developed in Drosophila are almost immediately then extrapolated to humans. It's really fascinating.

Hughes: Could you see that immediately?

Rutter: No, not immediately, but the qualities of the system were obvious. If one tried to do comprehensive genetics on something like a mouse (and there were several centers in the United States), it was obvious it would be too costly in time and money to have any truly penetrating genetic analysis. That might happen at the national labs and other places that were supported by a commercial enterprise, like the [Roscoe B.] Jackson [Memorial] Labs in Maine. Even then, with huge numbers of animals, one can't do penetrating genetic analysis routinely even today. Besides, the level of knowledge about Drosophila was substantial.

But there was an attempt to seek another "standard" genetic system. Sidney Brenner, a famous molecular geneticist at Cambridge, started a school studying the genetics of the nematode, C. elegans. C. elegans has interesting developmental characteristics. The fate of its cells is determined so one can map the origin of a given organ from a cell type. Just by the force of his own insight and personality, Sidney established a school that has contributed greatly to understanding development.

Hughes: What happened to the nematode emphasis?

Rutter: There still is an active research effort on nematodes. We have a very bright person in the department now, Cynthia Kenyon, who came from Sidney Brenner's lab and who works on nematodes.

Hughes: Was she brought in because of that interest?

¹ After more than a decade of debate, a division, rather than a department, of genetics was established in the mid-1970s at UCSF, in the Department of Biochemistry. For more on the division, see the oral history with Herbert W. Boyer in the UCSF Biotechnology Series.

Rutter: Yes, in part. From the beginning we tried to emphasize genetic mechanisms, and to relate molecular mechanisms to biological phenomena.

Hughes: That's very much the theme.

Rutter: That was the theme of the department. I believe it is one of the reasons why the department has continued to be very successful. This is very much the thrust of modern biology. The fundamental strengths in biochemistry and molecular genetics fueled everything from molecular structure-function analysis at the physical end of science to genetics at the biological end.

Hughes: I understand that you were very interested in adopting new technology. Please speak to how important that was to the progress of the department.

Rutter: Clearly, new methods had to be developed to approach human genetics; the methods useful for bacteria were too cumbersome and usually not applicable to mammalian cells.

Hughes: What are you thinking of?

Rutter: Well, the idea was to study transcription or translation, looking at the regulatory processes associated with cell-specific gene expression. One had to find new ways to look at sequence information and other molecular information. One could start by paying attention to the enzymes associated with genetic transcription. That was a subject which interested me because it was required in order to develop a simple in vitro system to analyze gene expression. But the major part of the puzzle depended on isolating specific nucleic acids of known sequence and function. So we spent a lot of time traveling to various labs throughout the world looking for people who wanted to solve this problem and had an idea how to solve it. So studies on the structure of DNA and RNA were a central issue in the department.

The Influence of European Molecular Biology Laboratories

Rutter: There was a great scientific group in England, at Cambridge, that involved not just [Francis H. C.] Crick and Brenner, but also Fred Sanger, as well as x-ray crystallographers like [John C.] Kendrew. This group had been built up over time, supported by the MRC [Medical Research Council] of England. These laboratories were a model. They seemed to operate more cooperatively than labs in the United States.

Hughes: Why?

Rutter: Of course, to some extent this depends upon the individuals. However, the scientists were supported reasonably well and given essentially complete freedom. The UK set up real research institutes whose main job was to perform research, not to teach in the classical sense. After [William] Bragg's discovery of the basic fundamentals of diffraction, they set up scientific groups to study diffraction. Around the old Bragg laboratory, there developed a school which first determined the structure of the proteins, myoglobin and hemoglobin. This became the world center of macromolecular structure [research].

Of course, when Watson wanted to do DNA structure, England was the logical place. The molecular activities coalesced around Crick and Brenner and Fred Sanger, who eventually won two Nobel Prizes. Fred was a tremendously impressive man who focused on methods for studying biological macromolecules, first amino acid sequencing of proteins and then sequencing of nucleic acids.

In trying to build a group here, we borrowed heavily from the idea and technology developed by this group, and tried to attract their best young people.

Hughes: Was the attraction money?

Rutter: Not really, although the level of support was an issue. I spent a fair amount of time in England getting to know the best young people. We tried very intensively to hire a guy named Richard Henderson who is still there. Henderson and Nigel Unwin had begun working on the structure of organelles.

Hughes: Did they come?

Rutter: They didn't come here. Unwin came to Stanford for several years, but eventually returned to Cambridge. They stayed there for the best reasons in the world, that Cambridge was and is a fabulous place to do science.

I mention this to emphasize that there were other superb places to do science; we didn't have the best situation, and we weren't always successful in recruitments. Sometimes, in fact frequently, the recruitments were carried out over a period of years. We needed to constantly improve our environment and compete with the most attractive situations. Of course, we were trying to recruit individuals who would have progressively more successful careers. We didn't try to recruit Sanger or Crick but rather the young and talented people who weren't yet recognized

and who basically had to face the giants as their careers progressed.

We were trying to get a large enough group here so that it could act cooperatively to be a major force. We hired two x-ray crystallographers, not one, because we wanted to develop a program instead of having a "representative" of a field. I think we were the only department in the United States that had this philosophy.

Hughes: Did people come eventually from Cambridge?

Rutter: No. The two crystallographers came from Caltech, and Edmonton, Canada, but one of them had trained with a key member of the British structural community. We paid much attention to Fred Sanger's research because methods were critical for DNA sequencing.

Hughes: Did he make those methods freely available?

Rutter: Oh yes. Fred didn't go around talking and giving workshops. He wasn't a flamboyant character, but he was very friendly and helpful. It was quite possible to have people work in his lab. He was cooperative as long as he believed there was a serious scientific purpose. He was very helpful, frankly, as was everybody else.

European Models for the Department

Rutter: Besides the UK's Cambridge, Oxford, and London labs, another exciting laboratory in Geneva, Switzerland was training many outstanding young people from the U.S. There we found Howard Goodman.

Hughes: What is the lab?

Rutter: It's a lab at the University of Geneva headed by Alfred Tissieres. There were three or four senior people, but it was run as a group lab. In addition, there was a famous institute in France, the Pasteur Institute, illuminated by [Jacques] Monod and [François] Jacob and others.

We tried to create at UCSF an adaptation of those successful labs--a very interactive dynamic atmosphere that wasn't dominated by a single individual. Clearly, there were areas of consensus and also of sharply individualistic opinion. Because of the rapid expansion of biological frontiers and methodologies, this

department couldn't be a typical biochemistry department comprised of carbohydrate chemists, protein chemists, enzyme chemists, elaborators of metabolic pathways, et cetera. Here the interests were too diverse for true cooperation. We wanted to organize our activities around a theme of major proportions where everybody more or less knew what everybody else was doing and hence the potential for collaboration was high.

Hughes: Did you come to UCSF with this European model in your mind?

Rutter: Yes. However, I didn't define it as a European model.

The reason why UCSF was attractive for this kind of development was that there were many open [faculty] positions. I felt that a collective approach was required to extend understanding of simple organisms to complex organisms. One didn't know from which branch of science the solutions would come. The issues were multidimensional; there wasn't just one simple solution. There had to be chemical solutions, genetic solutions, structure solutions, biological solutions. If you didn't have all of these approaches working collectively, the risk would be higher. It would take a longer time. This feeling gradually crystallized in my mind. So after all the declining of the UCSF job offers, I finally decided to go to San Francisco and see what I could do.

Hughes: [laughter] Too hot an opportunity.

Rutter: Right.

The Biotechnology Industry

Intellectual Property and Venture Capital

Hughes: Is Sanger's generosity characteristic of science today?

Rutter: Few labs are closed, but there has been a major shift towards protection of intellectual property. By and large, labs are concerned about intellectual property. Really, an amazing change in the past ten to fifteen years.

Hughes: Labs in general?

Rutter: All over the world, for sure. In the United States, probably more than in Britain.

Hughes: Why the trend in that direction?

Rutter: Because intellectual property rights are perceived as being very valuable to both the individual and the institution.

Hughes: How do you feel about that?

Rutter: I have mixed feelings. There are some aspects that are very good about it.

Hughes: Such as?

Rutter: Venture capital is now a major source of support for science. For example, companies are established to work on fundamental mechanisms of transcription in mammalian cells. This process is quite far away from a product. So venture capital is an alternative way to support the work. This is virtually a uniquely American approach. The venture capital approach is not well developed in other parts of the world. In addition, scientists via this mechanism can be very well rewarded financially for their work. This has its good and bad aspects.

We at Chiron spun off a basic program in cancer, the molecular mechanism of neoplasia. This independent program--the company is named Onyx--brought together a group of scientists from various parts of the country. Harold Varmus and Henry Bourne from UCSF are part of that program. Maybe a dozen scientists from various parts of the country are involved as advisors. The core group came from Cetus.

When Chiron and Cetus merged [1991], we couldn't fund the work at a high enough level to support everybody; venture capitalists supported it. Now they are going to try to make some money out of it, which might not happen without a proprietary position on some of the processes. Value may also be derived from understanding the fundamental mechanisms, so that strategies for halting the neoplastic process might result. This venture capital approach provides a balance to European funding mechanisms.

European Models of Funding Science

Rutter: Europeans have a tendency to make big commitments of resources to individual labs. In the late 1960s, we began working on the enzymes that were involved in transcribing DNA to RNA, the RNA polymerases, and discovered the three polymerases. During the same period, Pierre Chambon, an outstanding French scientist who

had worked with Arthur Kornberg¹ at Stanford, made similar observations, but later than we did. Chambon developed a major research program. We named our enzymes RNA polymerases I, II and III. He named his enzymes RNA polymerases A and B. For nearly fifteen years, the Europeans mostly called the enzymes A and B in the literature, while Americans called them I, II and III. Now there is unanimity.

Gradually Chambon has become the dominant scientist in France. The French are trying to push him for a Nobel Prize, so he has an absolutely huge lab. Today he may have five hundred people in his lab. Much of it is supported by the French government, but more recently part of it is sponsored by a U.S. drug company, Bristol-Myers Squibb. This strategy of funding gives the individual immense resources, both in terms of people and technology, to work on a problem.

In the U.S., a single laboratory can't compete well with our standard funding mechanisms. So more recently, some of the best scientists have gotten together and set up companies, backed by venture capitalists, to work on, for example, transcription factors, that is, the factors which regulate the expression of genes by interacting with the regulatory regions in the DNA. This is the path resulting from the discovery of these polymerases, and the study of their role in transcription. These factors interact with the regions which regulate the polymerase action. The program followed from what we started in the late sixties with Robert Roeder, now at the Rockefeller [University]. One of the key scientists, Steve McKnight, who was at the Carnegie Foundation at Johns Hopkins, gave up his job to come and work in this little company.

Hughes: What is it called?

Rutter: It is called Tularic, from an Alaskan river where several of the key scientists, one from Genentech, David Goeddel, the other from Berkeley, Robert Tjian, would often go fishing.

But the main factor is that a proprietary position on a key gene or gene product can provide a funding mechanism from commercial sources. This will eventually lead to new knowledge and also more practical work.

Hughes: It's the "eventually" that is the catch, is it not, with venture capital?

¹ See the oral history with Arthur Kornberg, M.D. in The Bancroft Library Series.

Rutter: Well, yes. The danger is that the appetite of these companies for resources continues to increase exponentially, whereas the funding capability and the interests of the venture capital groups are definitely transient. Venture capital companies are both a strength and weakness of our capitalist system. They provide funding, but they are interested for the most part in selling to the public market and getting out and doing another deal instead of building something over a longer period of time. They make enormous amounts on these transactions. If they tended to keep their money invested, hopefully not by laws but by tradition, then I think they would organize the companies better and think more clearly about building a sustainable enterprise. There should be rewards for building a sustainable enterprise.

The venture capital group coupled with the investment banker group provide elements of extraordinary strength to the capitalistic enterprise, but they also have a negative influence because they are so transaction oriented. They make enormous amounts by change. They present an arguable platform for a public company (and make a lot of money out of it). They underwrite an offering in legal and financial details; they sell it to the public, and then there is an even greater appetite for additional new ventures. The venture and banking groups continue to search aggressively for situations which can conceivably be presented for market. In my view, the incentives and rewards are too high for those facilitating or servicing the public or private capital markets.

Hughes: I would think that the time frame of the two components would always be at variance.

Rutter: You mean the time frame of discovery and of commercialization?

Hughes: Yes.

Rutter: You're right.

Hughes: And those behind the two components have different motives.

Rutter: Individuals have complex motivations. But when you asked the question about establishing a proprietary position, an intellectual property base for a commercial development, the lure of being both rich and famous is pretty intense. It's not as crass as it sounds; new scientific information frequently can be coupled to a commercial goal.

For example, research on mitosis is hot right now. Some of the most impressive scientists at UCSF are now starting a company, Mitotics it's called, based on new information about the processes

surrounding cell replication (mitosis). People who wouldn't have thought of starting a company some years ago--Marc Kirschner, Mike Bishop, and other academics--are involved. This is a result of discoveries of underlying mechanisms and realizing that so much of the pathology of human beings, for example, cancer, is associated with uncontrolled mitosis.

Hughes: But as usual, it's not unifactorial. A company such as Mitotics probably wouldn't have been necessary in the early fifties because funding for science was easier to obtain. In a sense, isn't the bottom line money, or the lack of it, that moves people towards industry?

Rutter: Money in two ways. One is the necessary resources to carry out competitive research. That's why I was making the comparison between Pierre Chambon and those in the United States who have tried to compete with Pierre (me, for example). So that's part of it, yes. On the other hand, there is actually the bona fide issue of societal impact in the translation of an idea to clinical utility and practical reality. Independent institutions, not universities, are most effective.

Biological Information Becomes Applicable

Hughes: Simplistically, biology had become commercially applicable. Classical genetics in the fifties and even early sixties hadn't developed to the point of applicability.

Rutter: Right. And classical genetics was more applicable to agriculture than to human beings. These processes become manipulable when the level of understanding is deep enough. The greater the amount of information, the more networks one can establish and therefore the more practical it becomes.

So to get back to the question: there are several reasons why there is so much patenting. One is the understanding that there can be a practical benefit, and thus the desire to obtain recognition for the lab and also for oneself. If there is some gold in the hills, and you happen to get a chunk, well, there is no point in leaving it in the ground if somebody is going to pay you for it. That's what the biological sciences are, a tremendous hotbed of intellectual and commercial ferment, with the possibility to discover one of the mysteries of life and also get rich quick.

Hughes: Does altruism enter in at all?

Rutter: Yes, of course. Motivations are complex.

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Rutter: Some of the early biotechnology companies were based almost purely on hucksterism. There was a young faculty person in pharmacology named Martin Apple who started IPRI, the International Plant Research Institute. Its goal was to genetically transform plants. Apple had a strong scientific imagination and a flair for selling. In addition, there were dedicated scientists at IPRI. For a relatively poor scientist, there was the vision of sudden riches.

For example, Martin once offered me a couple of million dollars a year to come work with him. He had raised a lot of capital from the public market, and he needed someone to display to the public to keep their interest while the company was working on miracles. When it came to science, he stretched the truth; he was not rigorous. In fact he was a phony. The reason I mention it is that it was close to home, UCSF. Martin wasn't a successful scientist at UCSF. But he had a strong entrepreneurial instinct and was savvy about many aspects of science. But he didn't have the discipline which is necessary to be truly successful.

Carrying out a novel project for the good of society and creating a business and personal wealth is immensely appealing. Many people are totally drawn into the romance. One gets a mixture of people with both high ideals, sophisticated understanding, and the more basic instincts. That's why intellectual property considerations are both good and bad. Biotechnology is a microcosm of great talents and charlatanism, sometimes in the same individual. It's more or less what you would expect.

In the commercial world, technological companies are oriented around the group of technologies on which they were founded. In this area, they have a high degree of sophistication and people who understand the technology and the business related to that technology. Very few companies can follow rapid developments in their field or move into another discipline. Even great companies are to some extent determined by their past, not oriented to their future. So companies need the resources and the commitment to proceed in new directions along uncharted paths and to overcome the resistance and prejudice of other scientists and mature companies. That is essentially what has happened in this area where you absolutely need new technology and also new and independent market forces.

Framing Biological Questions in Mechanistic Terms

Rutter: Most people don't understand that once one can frame a question in detailed mechanistic terms, one can soon find a solution or several solutions to the question. The game is to try to get there first with the most elegant and decisive solution.

Hughes: So every biological problem is soluble?

Rutter: I believe, eventually. Consider the biological problems which are not soluble today, for example psychology. Psychology is not approachable because we can't frame it in a sufficiently mechanistic way that we can obtain answers with today's technology. We gain information about psychology by observation and inquiry, and by using various indirect methods of increasing sophistication. But we have little structural and mechanistic information at the molecular level on which to base a theory of behavior.

Through genetics, one can begin to get useful information. Drosophila and cockroaches, Aplesia, display interesting neurological characteristics which can be studied. Sooner or later, then, through molecular genetics, molecules--proteins--which regulate behavior in these simple systems are discovered. Then one finds there is a similar molecule in humans which probably has a similar function.

When a process can be understood at a sufficient level of detail so that a specific hypothesis at the structural or molecular level can be posed, then the question can eventually be resolved. This was the situation which existed in the early days of the department. One could formulate questions in very specific terms and hence there must be a solution. To understand human genetic systems, technologies were required to obtain pure DNA or RNA sequences and to use the sequences in simple expression systems. The cloning of the insulin gene was useful only if one could characterize the sequence and study its biological properties. Howard Goodman is the person we finally attracted to UCSF to develop nucleic acid methodologies. He didn't do it alone, of course; there many many good, young scientists in his and other groups, who were eager to work in this area.

Teaching ##

Initial Subordinant Role in the Department

Hughes: Do we have the department structure in place so that we can now talk about the teaching program?

Rutter: It was important to assume some executive control of the department. The department was disorganized; its control was diffuse. There was so much distributed power, nobody could really use the resources which existed to move on and establish a strong research base. I was much more concerned about doing that than to establish a distinguished teaching program. I felt that teaching of medical students was probably being carried out on the borderline of adequacy. However, there wasn't significant graduate teaching. The development of a scientific team took time and the accumulation of people with good scientific taste was paramount. This couldn't be done overnight.

Hughes: Did people outside the department object to the research emphasis, to the possible detriment of the teaching effort?

Rutter: Yes. And the students reacted as well. For a while, the teaching by the department didn't really match up to the expectations of the school. At one level, the school wanted and needed more effective teaching in modern biochemistry. They got that, but it wasn't delivered in polished style. During this time, we were so busy trying to get the science and the infrastructure organized that we couldn't spend all of our time teaching. I believe it would have subverted what I considered our main mission to be. So we had to develop a teaching program with the same individuals we were trying to replace. That was not always easy to accomplish. But in general the individuals were of good will and took their responsibilities seriously. Further, when it came right down to the bottom line, the clinical departments understood and were patient.

Hughes: Were they?

Rutter: I believe the heads of the departments at least understood. That didn't mean that all the faculty were patient. We got hell from the medical students over a period of time; I couldn't believe it. Even great instructors like Gordon, who was so personally charming and articulate, got trashed by the students. He would come to me and say, "Well, I'm human too. Why don't these guys tolerate me?" [laughter]

W. J. Rutter as Teacher

Rutter: I obviously had to do some teaching myself. But I usually did it extemporaneously, so sometimes things went well and sometimes they didn't.

Hughes: Is that because you prefer to be extemporaneous or did you not want to spend the time to prepare, which obviously would take time away from other things?

Rutter: I persuade myself it's the latter, but in reality I should have the discipline to prepare. It's a question of deciding what's truly important. I consider this to be one of my bigger failings. I rarely spend the time to develop a good talk. Sometimes I do and then sometimes I don't. It just depends on the pressure of other events.

Hughes: Do you like teaching?

Rutter: In fact I do. I especially enjoy teaching in small groups and with individuals. Repetitive teaching is not something that interests me, but I like analysis and articulation of ideas. Always, one gets some new ideas from the process. Another of my own failings: I get caught up in new ideas and usually transmit these to the audience. I usually transmit information and various interpretations, not a straightforward approach that is more appropriate for the usual medical student.

When we came to UCSF, there were laboratory courses for medical students. Of course, it took a lot of effort to run a lab and the students had no appetite for lab work. They wanted to get to the patients.

I had had the experience of developing a lab course at the University of Illinois. The head of the department, I. C. Gunsalus, wanted to develop the lab course and used the younger faculty to develop experiments. He eventually published a book under his name and got some royalties, I learned many years later. Developing the lab course was a disaster. One spent all of one's time working out the details of experiments that could be carried out by students. One would try to make each experiment foolproof or idiot-proof. I considered this a total waste of time for somebody who wants to get on with real science. I also felt it was a waste of time for the students and never liked that kind of busy work myself. When you realize that only a small fraction of the students benefit by this practical work, it seems a waste of resources. I preferred to give a higher level of instruction to

the fraction of the students who were interested than to provide everyone with training at a lower level.

This approach had downsides as well. Part of the justification for the number of people in the department was based on the teaching load and these laboratory commitments. Space in the department was also allocated on the basis of the teaching program. These big labs were part of the space allocation. So the challenge was to keep the faculty, keep the space, and not do the teaching. [laughter]

Using Research Labs as Teaching Labs

Hughes: How did you do that?

Rutter: We made the argument that we should really encourage medical students to come into the research labs. So our research labs were in fact teaching labs. That wasn't a phony argument; I believed it. If UCSF was going to be a premier school, we ought to attract high quality students who were interested in academic medicine--M.D./Ph.D. candidates or M.D./M.S. candidates. Our position was different from that of a typical medical school: if we were going to be a first-rate institution, it was essential to populate academic departments in other medically oriented institutions. Hence, it was important for us to establish programs that were consistent with that mission. General laboratories didn't contribute to that mission.

We were one of the first places to teach by workshops. Let's say there was an interesting new scientific or technical approach. We would simply ask the scientists from the best labs who were developing the science to come in for a week or two and then give a course which everybody could take. We'd set it up in whichever labs we could set it up. Students, faculty, postdocs, whoever, could use it then. This approach really works; we do it now. Workshops are usually given on weekends so that all can attend. We get several hundred people to come and they are very popular.

Clearly, at the time we started [as chairman], a major issue was the quality of our graduate students. We couldn't compete with Berkeley; we couldn't compete with Stanford. So we had to create a program to get good students prior to the time that we developed a luminous image. One of the ways to do that was through the medical program. Some of the medical students were

attracted to science. We argued strenuously for an M.D./Ph.D. program or some kind of professional program in science.

Hughes: Which had never existed?

Rutter: No. So we developed those two basic strategies of education.

Hughes: What about the postdoctoral program?

Rutter: At first, the postdoctoral program was more or less related to the individual faculty programs.

Hughes: Had there been a postdoctoral program before you arrived?

Rutter: Oh yes. For sure, there were postdocs in individual labs. But the active labs and resources were dispersed throughout the school. The Cardiovascular Research Institute dominated UCSF research. Manuel Morales and his retinue were there. There were many postdocs in Choh Hao Li's lab, but they were not in the department.

The postdoctoral program was an important issue for the younger faculty who came to UCSF. Postdocs and students were necessary to carrying out their research programs. Professors couldn't do it by themselves. Creating an environment to attract talented people was the major issue. The educational program was segregated into teaching medical students, and teaching graduate students and postdocs.

Teaching Medical Students

Rutter: The school had to be convinced that we were doing a good job with the medical students, despite the fact that the clinical departments were tolerant and supportive of us. Still, we had to mount a program that was judged acceptable by the students and was hopefully a good program in its own right. We oriented our teaching toward medical issues and moved away from classical biochemistry teaching.

Hughes: Did you find it easy to move towards clinical problems?

Rutter: Oh yes, I was fascinated by this subject. That was one of the reasons I came to UCSF. I told you about my early interest in medicine, parasitology, and galactosemia. So I was fascinated, always, by medical issues. Furthermore, appropriate cases were available for educational purposes and were easy to present to the

students. What was not so easy to translate was the vision of future approaches, that is, to give them an idea that things were really changing dramatically and that they could participate. We emphasized that in their own careers new information and new concepts would lead to enormous changes in the practice of clinical medicine. Students were obviously more interested in the realities of the present information and getting through their courses. And of course they had a huge amount of information to process. Gaining perspective was understandably not high on their list.

We had the problem of team teaching. We got quite a few clinical people to participate in the clinical orientation sessions. Then we got various people from around the school to give lectures. We also had the delicate problem that we wanted these people to teach but didn't want to give them joint appointments. So we wanted to "clear the decks," not give joint appointments, yet get the teaching job done. Luckily, it worked out reasonably well. People were interested in the subject and were cooperative. There was always a chance that they might be appointed to the department. If we had given appointments in the department, we probably would not have been so successful in getting them to teach. [laughter]

The Graduate Curriculum at UCSF

Rutter: Starting a graduate curriculum was another matter. The graduate school at UCSF was mediocre, virtually from top to bottom. There weren't any general courses to provide fundamental information that were mainstays of the graduate program. It was typical in those days for an individual to teach a course by asking others to give the individual lectures. So the head of the course brokered the teaching program, and one would get invitations to lecture in x, y, and z course.

Hughes: There was no cohesion.

Rutter: There was no cohesiveness in the program. To some extent, the professors were not interested in a coordinated program. One could give the same lecture in ten different courses, presenting information at more or less the same level. You can see what the net result was: superficial science presented redundantly, the presentation of specialized tidbits of information.

Hughes: When did the graduate program get off the ground and why?

Rutter: I believe our department was the key to that. But it was not simply due to members in our department. Individuals in the Department of Microbiology played an important role, in particular, Michael Bishop.

At first, neither Microbiology nor Biochemistry could attract good students. We proceeded to first attract students to Biochemistry. I remember, we used to send out brochures and give them out whenever we gave seminars--we used to give a lot of seminars. We'd always be recruiting for graduate students when we gave seminars.

Hughes: And putting forward the multidisciplinary approach?

Rutter: Yes, describing what UCSF was all about. That attracted graduate students more rapidly than most people thought was possible. Then the people in Microbiology, especially Mike Bishop, Herb Boyer, Harold Varmus, and Leon Levintow, and others in the school, participated in the teaching program. The program coalesced into a single program. These people were given joint appointments.

When did that happen? It happened in the early to mid-seventies. We had a program that was flourishing by 1975. After Gordon Tomkins' death in 1975, we were faced with recruiting distinguished and charismatic people. In the 1975-76 time frame, I was always scouting for good people.

Hughes: To fill Dr. Tomkins' shoes?

Rutter: Well, Gordon was a marvelous charismatic person.

Hughes: So he attracted people.

Rutter: He attracted a lot of people and helped to create a cohesive attitude toward science in the school. With Gordon here we focused on attracting younger individuals with great potential. When Gordon died, we needed another senior person for sure, or more than one. We ended up recruiting Bruce Alberts and Marc Kirschner, both from Princeton. Bruce was and is a remarkable scientist, with broad perspective. He was also extremely interested in teaching. The department and the school took another step forward. He and others from the Princeton group, Marc Kirschner and Keith Yamamoto, were more teaching oriented than I was, for sure. This was tremendously good for the department.

Bruce with others eventually produced the classic text, Molecular Biology of the Cell.¹ This formed the basis of the broad approach to cell biology and was at the core of the teaching program. This I believe confirmed the eminence of the department in science and teaching. Graduate education had progressed from a single course supported by seminars, to a tremendously expanded coursework and seminar program, and workshops. We didn't recruit the great old figures of science, but for several years, as I told you, we brought in people like Fritz Lipmann for half a year at a time. We wanted to enrich our environment by interacting with great scientists of all ages. They would give courses and seminars and interact one on one with people. I felt this was the best teaching you could possibly get. Of course, not for medical students, but for graduate students and postdocs it was super. We could do this because we had budget flexibility. We hadn't filled up our positions, so we could use the funds at our discretion.

The Department's Enterprise System

Rutter: Putting the department on an "enterprise system" was crucial for all of this.

Hughes: What do you mean by an enterprise system?

Rutter: The clinical departments operate as individual enterprises. They're group practices. So they receive so much money from the school, and they get so much money from their practice. The school takes a cut and then they get to use the rest for their own purposes. They could, for example, distribute it as part of their salary.

Now, the school had the problem of variable pay in the clinical departments. For example, surgeons and radiobiologists were extremely well paid, whereas pediatricians would earn less. In order to transform the institution to a true academic institution, one had to establish a system which acknowledged differences in pay for the various specialties, but eliminated individual pay-out programs. One shouldn't use the academic situation, which in principle was supported by state and federal contributions, to make money.

Hughes: Was variable pay a problem at UCSF?

¹ Bruce Alberts et al. Molecular Biology of the Cell. New York: Garland, 2nd ed., 1989.

Rutter: At one time it was. Yes, indeed. In certain departments, individual compensation was linked directly with their private practice. So one of the key issues the clinical chairmen took on was to get a salary range plan. That decoupled personal income from their contributions to group practice.

Having watched it develop and watched all the politics that was associated with it, I wanted to free ourselves largely from control by the school (the dean). So I negotiated for an enterprise budget just like the clinical departments'. The idea was that we had services to provide to the school. I had a budget that prospectively dealt with those services. As long as I performed the services more or less adequately, then I could use the budget more or less freely, which would mean that if a faculty member was supported from another source, by the NIH or the American Cancer Society or whatever, then we could use his salary contribution from the state to support other programs. That was just tremendously important for us.

Hughes: Was that easy idea to implement?

Rutter: It wasn't easily executed, but it wasn't so hard to sell eventually because how could they refuse? The precedent was there in the clinical departments.

This was one of the concepts that Julie Krevans supported that I thought was extremely useful, and Philip Lee, the chancellor, also supported this approach. I think I initiated the practice with Stu Cullen, the dean prior to Krevans. Stu Cullen was an anesthesiologist and was familiar with clinical practice. He was by nature a very independent person and thought there was nothing wrong with the concept. Why not? We were very fortunate. It would have been very difficult today with the school's tight budgets.

There were university rules which restricted the use of the money. However, in order for us to operate the department's programs, we had to have some free money.

Hughes: Did the enterprise system apply to the other basic science departments?

Rutter: Not at the time, but I think eventually it might have. I didn't advertise it; we didn't want to create a big ruckus. At that time, less so than today, each department had its own budget and had to account to the school for expenditures. But there was no real cooperative analysis among the departments about standard practices and controlling expenses. I told you about the meetings of department heads. We began to discuss some of those issues.

But that was far after the time that we had the system operating in our department.

The school was more concerned with deficits than it was about our expenditures. Hence, I went to some length not to be in significant deficit. I didn't argue for many of the subventions to cover overspending. The other department chairs would come to the dean at the end of the year to haggle because they had always overspent. So, in payment for budgetary freedom, I didn't ask the dean to bail me out. This allowed us to do unusual things. I believe it is a tremendously useful principle to give budgetary freedom to the various departments, obviously consistent with some kind of principle for expenditure and an overall audit system.

How did we get free money? We frankly used every avenue at our disposal, from gifts, grants, and awards to using departmental property. I will illustrate: When I came here, the department had a stockroom filled with antiquated supplies. Among them were some platinum boats that had been used to weigh out material for the determination of nitrogen via the Keldal procedure. Do you know about these methods?

Hughes: No.

Rutter: In order to measure nitrogen in biological materials, they were combusted in Keldal tubes, eventually leading to an ammonium salt. The combustion took place in platinum boats. Obviously we didn't need the boats, and the university had no way to sell the boats, so I went down and sold the platinum boats and with the funds established an account in the name of the department. It was a bona fide account, required two signatures, et cetera, for the release of funds, but it was an off-line account and therefore was not subject to university rules. We also added to the account honoraria and sometimes awards of various types. This allowed us to entertain visitors and to purchase things that otherwise would be difficult to purchase, and a myriad of other things such as to help pay transportation for new recruits. The university policy was to pay for only half of the moving expenses. You couldn't get people to move under these conditions. They just didn't have the financial resources. So you had to find some way to help them without making a big deal of it.

The general problem was that the academic enterprise runs on pretty scarce resources and frequently this shows in the institution. But individual scientists have quite sophisticated tastes, so naturally they want to enjoy themselves, especially when they come to San Francisco. They like to go to a good restaurant. We tried to make up for the lack of style in the facilities of the school. It was bad enough to walk down those

old green halls. So we tried to get everyone to think positively about the school and its environment as an attractive place to develop a career. Economics and space were the fundamental driving forces, as well as support from the clinical departments, which had a similar vision of the school. Those were the key elements to success. It just wouldn't have worked unless we had all of them working for us.

More on the Department

Hughes: Another component of departmental activities were the Asilomar meetings. I believe the first one was in 1975.¹

Rutter: That was another way we differentiated ourselves from others and built. All of our group went to scientific meetings. There were the Gordon conferences on various topics. These conferences are held in boys' schools in New England, usually in isolated locations in Vermont and New Hampshire, with terrible food, terrible beds, and usually a shared room. The scientists go usually for a week. We all liked to go to those places, especially to meet people. But we soon recognized that meetings of our own group could be as stimulating and could help develop cooperative programs, provide appropriate critiques, et cetera.

UCSF itself wasn't a good meeting place. The atmosphere in the buildings was bleak. So we eventually decided that we should have our own departmental meetings, but we needed to pay for them meetings, because clearly people couldn't pay for the meetings themselves. The department had a tough time but we managed to scrounge the funds with time. We realized that the Asilomar meeting was central to our main educational functions. It was a workshop off-site. The Asilomar meetings turned out to be marvelous experiences. Great science, each major professor talked, much informal discussion, lots of socializing, dancing, even skinny-dipping. It was just a way to have a lot of fun with people.

Hughes: Was it just the department in the beginning?

Rutter: Yes.

¹ William J. Rutter. "Report on the Department 1975". Department of Biochemistry and Biophysics, University of California, San Francisco, Annual Report, 1975. Published May 1976.

Hughes: Then it expanded.

Rutter: Yes. Now, of course, it's virtually the whole basic science program at UCSF. It has become so popular. People are honored by presenting there. The Asilomar space is better now than it was then, but it is still limited.

We were concerned to foster interactions between the research groups. Even though we met together on the campus, we didn't have enough time; we were very busy. We needed to foster interactions from the professors down to the level of graduate students and postdocs. We needed a good way to more penetratingly monitor the science programs and subtly influence the programs that were not going so well. We also had department seminars, of course, but they were not a really good vehicle for subtle criticism.

Hughes: How does monitoring operate at Asilomar?

Rutter: Well, each of the groups presents their ideas and data.

Hughes: So it becomes self-evident where the deficiencies are.

Rutter: More or less. In a walk on the beach, one can talk about many things in a nice, casual, nonthreatening way. It's totally different than sitting in one's office.

Hughes: What did you do about nonproductive people or not sufficiently productive people?

Rutter: Some of them left, with help. Others stayed and became progressively more productive. This is a great system to develop scientists and science programs.

A Cooperative, Interactive Approach

Rutter: It's difficult now not to be successful at UCSF, if you have any of the requisite elements of success, because the students and faculty and the cooperative spirit are so good. This is a place to succeed. That's the reason we can attract better people than any other institution. Further, our success has, in a sense, had an impact on other universities. Other universities, including Harvard, have changed their style. There was a great rumbling when we were successful in out-recruiting Harvard.

It was our cooperative and supportive, down-to-earth style. We weren't always trying to get rid of people. In the Harvard system, as you probably know, each science professor has one or two assistant professors in his field. They usually are given five-year appointments. Most of the time these young people leave because, when Harvard recruits, it always demands that the individual be the best in the world. Well, that's a very difficult criterion on which to judge a young scientist. So by having that constraint, Harvard gets the pick of the crop later. But the younger guys don't want to stay there because the probability of their getting tenure is low, and during that time period they are basically beholden to the full professors. Until recently, they were not truly part of the academic enterprise; they were sort of apprentices.

From the beginning, we took another approach. We were supporting people whom we believed could be stars later on. The more mature ones of us were just trying to facilitate a balanced program. We were obviously competing, too. It was a good atmosphere.

That environment didn't exist at Stanford either. Stanford was more or less an exclusive club. When Arthur [Kornberg] came with his group from Washington University to Stanford, they isolated themselves from the others. It wasn't an interactive place. It was absolutely great for postdocs and students, the best in the country on an individual by individual basis, but it was perhaps the most closed place. It was a tremendous department and produced two Nobel Prize winners. But it didn't catalyze scientific development or strongly influence the academic environment. As a result, Stanford Medical School had departments of unequal distinction. The greatness of the Department of Biochemistry didn't extend to the rest of the school. It was difficult for the other departments to play off that strength because there was little interaction.

Our program was exactly the opposite. We tried to develop the whole environment.

Hughes: Was that inertia on Stanford's part, or was that policy?

Rutter: That was deliberate. It was not without wisdom either. One of Arthur's great strengths is his single-mindedness and his sense of quality: don't try to do more than you can do; just play your game

and play it well. Our approach was more risky: try to do more than you can do, and then make choices about what the priorities are. Each has its rewards.

Our approach required a highly interactive, supportive, focused, multidisciplinary, quite entrepreneurial, uncomplicated academic environment. Of course we were lucky because we could bring in people at the right time. We were growing when other people were not. So we were in a different dynamic phase.

The Importance of Contiguous Space

Rutter: Just a word about the essential importance of contiguity and space in the development of the environment. It obviously follows that for close interaction and for psychological or personal support, space should not be fragmented as it is in most schools; hence, the development of the educational plan, the elimination of nonproductive coursework, and starting a distinctive teaching program. The tensions between the various departments over space were really related to the demand for contiguous space and a close environment.

Contiguous space was important, but also the design of the space. I spent a fair amount of time designing the space in order to have common areas for equipment. We shared equipment so that people from the individual labs and the professors naturally ran into each other. On each of the floors, the labs were situated on the outside and the shared space was on the inside. We developed common core facilities. At first we had a stockroom. But eventually we eliminated it because we ran out of space; we distributed the reagents in the various labs and shared. In all situations, we tried to develop, through the department, instruments and technological approaches that would not have been possible within the individual labs. The concept is self-evident, but it doesn't always work that way. Our economic sufficiency helped greatly.

The fact that UCSF was not such a developed school made it easier to compete for resources. The chancellor and the dean were usually in a position to help a good program. That was a strong element in our success. We had the space, we were able to use the space, and we could develop facilities.

Later on, during the initial phase of genetic engineering, it was extremely important to have a P3 containment facility for recombinant DNA research. When we decided we needed such a

facility, we constructed it immediately. It wasn't so expensive--maybe \$50,000. But we could say, "We have to do this next week; let's do it." We could scrounge up that kind of money. Today it's much more difficult in most departments, and of course containment facilities are about ten times more expensive.

The dynamics of the department were different. It was a little bit like a company, a little bit like Chiron is today. One of the reasons why it's been so easy for me to move to Chiron full time is that we have the flexibility to make our own decisions and carry them out with no artificial bureaucratic barriers--tremendously important in a competitive scientific environment. I also have to say business is not as competitive as science. [laughter] If you have been successful in the competitive arena of international science and you want to learn business, you will find it is not all that hard.

Hughes: That's not the usual image, is it?

Rutter: No. People don't usually recognize how competitive science is. Everyone is trying to beat you and will use every trick in the book. You have to manage your resources well because you are always under-resourced. You have to make priority decisions, and you try to cover your bets in many different ways. The requirements for success in business are not all that different.

Hughes: This is a retrospective realization on your part.

Rutter: Definitely retrospective. [laughter]

Fostering the Biological Sciences in the School of Medicine

Rutter: Now, with respect to the development of the biological sciences at UCSF, the Department of Biochemistry was a mini-school in itself because it covered all the most important scientific approaches in biology. We weren't just interested in molecular genetics. We also became a cell biology group because we were interested basically in the cell. There have been ebbs and flows. But it has been a department that has operated across the frontier of science. We always thought we knew where the various fields were going and tried to get scientists who would help or lead the change. As the department flourished, of course we ran out of FTEs and space. So how to grow? Clearly, it was by colonization of the other departments. [laughter]

Hughes: The only alternative.

Rutter: It wasn't a purely acquisitive strategy. It was based on the notion that all these fields were simply aspects of the same field, and many could be advanced by the same fundamental mechanisms. In a subject as broad as biology, one has to be more or less in control of all of the disciplines in order to solve complicated problems. So pharmacology depended on biochemistry and progressively molecular biology and genetics, and the same thing with pathology. All these fields become, one after another, susceptible to the use of modern methods to provide fundamental mechanisms. Older methods were largely descriptive.

In most of these departments, there was a residue of classicism, and also there were pockets of greatness in many of them. Without trying to be dictatorial about methodologies, the issue was to try to get the best people in those departments, the people who would move the science toward the future. In earlier times, the leaders would replace themselves and continue their favorite programs. To establish a "school" we had to be agents of change. One way was to get the department chairs together, try to solve common problems, and gradually begin to recruit together, provide some resources, give joint appointments to insure the quality of the new faculty.

That's when we realized that joint appointments were crucial. We ran out of FTEs, but we didn't run out of joint appointments. If a department wanted to hire someone, most of those people wanted to have joint appointments in Biochemistry. If we were involved in the recruitment, obviously we would agree to a joint appointment. This became a powerful force in developing the school.

Hughes: The benefits of joint appointments were now outweighing the disadvantage as chairman of not having ultimate control.

Rutter: That's right. By that time we had pretty good control, not just of the department but more or less of the basic science programs of the school. So we weren't worried about the same issues that we had to be worried about at the beginning. I think it worked to everybody's advantage. But, to harken back to Asilomar, we had to ask everybody with a joint appointment to come to Asilomar, so it became a big circus. But that also had its positive aspects. It became a tremendous meeting, but somewhat less personal.

This process of colonizing the rest of the departments with good people virtually secured the transformation of the school.

Hughes: Did you expect anything from those people other than good science?

Rutter: Yes, we expected them to be cooperative and interactive.

Hughes: They did whatever they wished to do in science?

Rutter: Yes, indeed, absolutely. We exerted some influence on the appointments of people and hence their field of interest. Scientific taste was a real issue for us.

Neurobiology was the first paradigm. Neurobiology was clearly a field of the future. Everyone was interested in the phenomenology, a totally fascinating subject. With the discovery of nerve growth factor, the first molecular approach to nerve growth, the field opened up. We cloned the cDNA [complementary DNA] for nerve growth factor in my lab. Clearly, we were interested in this subject, but we didn't have any way to develop neurobiology in Biochemistry. It was a field that couldn't develop with a couple of people; it needed to be interdisciplinary. We would have been in as bad a situation as Berkeley was at that time, with fragmented interests.

So we had to get a neurobiology group started. Physiology was the logical place; Pharmacology a second place, because neurobiologists existed in those departments, neurophysiologists with a bona fide interest in both physiology and pharmacology. We added some excellent people in both departments. The real problem was how to get a group that was large enough and dedicated enough to modern biology that it could make a big impact on the field. So with Fran Ganong we developed the idea of a neurobiology division and eventually recruited Zach Hall from Harvard and some others as well. Reg Kelly of Biochemistry was devoted to neurobiology, and Lou Reichardt, another superb molecularly oriented neurobiologist.

But those people required joint appointments. Zach Hall certainly wouldn't have come without a joint appointment in Biochemistry. So we played a strong role in recruiting them. Fran Ganong also benefited. Now of course, Ganong has retired and Zach is head of Physiology. But the close relationship with Biochemistry certainly helped to change that department. Physiology was a large department generated from a distinguished past and appropriately large in a medical school. Reg Kelly was a full member of Biochemistry, but he interacted very closely with that group. This way we colonized the interface.

The same thing happened in developmental biology with Henry "Pete" Ralston in Anatomy. Initially, they were interested in neuroanatomy. We helped that group, but also helped Anatomy focus some of its resources on developmental biology. We established a good working relationship with the new group in developmental biology which has now become outstanding. Pharmacology was the place for studying signalling systems, both in the CNS [central

nervous system] and also fundamental signalling systems associated with other physiological events, including cell replication.

The coalescence of these groups was centered in part on the technology which grew out of the department, but also on mechanistic strategies unique to each field: biochemical methods, biophysical methods, molecular biological approaches, computer-based data collection, all the things that make a modern laboratory a modern laboratory. The coupling of a new technology with the biological base usually produced a new level of understanding.

Money, Space, and Growth Problems at UCSF

Rutter: Now, with respect to support: in the late sixties and early seventies, at the time that we built the department, it was relatively easy to get money. These were the days when departments were built on NIH funds. One of the most powerful figures, Philip Handler, became head of the National Academy [of Sciences]. He had been head of the Department of Biochemistry at Duke and had tried to recruit me several times, first as an assistant professor and then as a professor. I used to have discussions with him from time to time. It was his contention that the federal funding of science would increase indefinitely at 15 percent a year. Of course, the idea is preposterous at the outset, but nevertheless his argument was that scientific research had such a small base, and that the economic growth of the country would be such that the 15 percent increase would be fueled continually by growth from a small base. A lot of people believed that. There was a lack of reality in the scientific community.

At UCSF, we were buffered from budgetary problems for a while because of this enterprise system. So when science funding began its downward trend, we could to some extent cope with it for a while, but our powers were distinctly limited.

The school's ability to grow and develop as a broad scientific institution was limited by its physical facility. Frank Sooy, when he was chancellor, made the biggest error of the century by agreeing to limit the expansion of the campus in exchange for an approval by the city to build Long Hospital. Whereas I supported the building of Long Hospital, I thought it was just crazy to limit our space. I argued as persuasively as I could that we should plan to expand and try to obtain addition space. In particular, I thought we should expand directly into Golden Gate Park, that is, establish a corridor directly to the

park and then say, Okay, now this is the limit of our expansion. We'd take care of the traffic needs and so on associated with expansion, and the neighbors could then live in peace, knowing that we wouldn't interrupt them. We would essentially build an enclave.

It was perfectly obvious when Frank made that decision that we would run out of space soon.

Hughes: What were his arguments?

Rutter: Long Hospital needed to be built. Of course, there was a very significant competition in the clinical community. UCSF needed a new hospital to remain competitive. Frank Sooy also maintained, "Things can always change." The ceiling would be lifted! But even at that time, campus growth was predictable, totally predictable. That decision which was very wise in the short run was disastrous in the long run.

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Rutter: It was necessary to plan for growth, hopefully to twice our current size.

Hughes: By this expansion to the park?

Rutter: By this expansion to the park. Astonishingly, absolutely nobody at UCSF was engaged in long-term planning. I don't think the situation was better at University Hall [UC Berkeley]. They are being forced to think long term now. I will give you an illustration. The dean [Rudi Schmid] several years ago, in 1986 or '87, started having executive retreats at Asilomar. I was asked to give a talk on the future of the school. As part of the talk, I decided to consider the demographics of the institution in order to ascertain where the school was going and what the needs would be in the next decade. I was surprised to learn that no one in the dean's or chancellor's offices had collected simple information such as the age of the faculty, their tenure status, and the likelihood of [their] leaving, et cetera. So I managed to get a couple of people to gather the data. The results were obvious. With the great influx of younger people coming in and the tenure system, there was a large wave of people growing old together. The retirements would not allow replenishment with young people.

Since we couldn't plan on an increase in the number of FTE's, one could predict absolutely what would happen during the nineties. Without intervention, the balance would shift to older

people, away from the younger people who have been the base for our continuing vitality. Without change, I predicted the inexorable decline and fall of UCSF from its preeminent position.

One doesn't have that problem with a big university like Berkeley. There the numbers of faculty are so large that things balance out. At UCSF, with the small numbers, one absolutely must solve that problem. Furthermore there is a space crunch. As the young people mature, they need more space and more high quality space. It was totally predictable that we were going to have the terrible problem which has been with us for several years.

Hughes: Did anybody listen?

Rutter: Sure. I finally wrote up the talk and it was widely circulated to the key deans and department heads. This was six or seven years ago. People listened, but nothing has been done about it. We're now in the midst of trying to build a second campus piecemeal and disseminate the campus.¹ Now one must create new mechanisms to bring in young people and to deal with space or else UCSF will decline to mediocrity. One might have a recrudescence another generation from now, but it will not be along the same lines. It is doubtful that UCSF could ever regain its lost distinction. The inability to deal with the fiscal realities and the physical realities of space is endemic in educational institutions. It's a tremendous problem at UCSF. It's a major reason that I'm doing what I'm doing now.²

At UCSF, there has never been a competent infrastructure. Regrettably this is true for the university as a whole. The university has never managed its resources and expenses well. There has been no mechanism to pay staff people adequately. The deans are chosen for their academic leadership. Many of them have no understanding whatsoever about costs, resource management, strategic decision making. The department heads also suffer from the same problem.

This is not so true for the hospitals. We have over time developed a very good and professional hospital management group, especially the director of the hospitals [William Kerr]. But the school itself has suffered tremendously, because I believe that

¹ As of 1997, Dr. Rutter is chairman of a committee to raise private funds for a second UCSF campus.

² In 1994, Dr. Rutter retired from UCSF and began to work full time as chairman of Chiron.

the people are financially unsophisticated and driven by politics, not realities.

Hughes: Is this truer of UCSF than of other institutions?

Rutter: I can't answer that fully because I know UCSF better than I know other institutions. I believe that the problem exists everywhere. I now know a little more about Harvard.¹ The Harvard machine is a very effective money getting and money using machine. Stanford has become, aside from hiccups, also a marvelous money generating machine. The financial mechanisms associated with money acquisition by these premier private universities is truly impressive. The state universities have never been inclined to develop their own sophistication about resources. Here UCSF relies only 15 percent or so on the state budget, but it acts as if all the funds come from the state. All of its processes are encumbered by the state bureaucracy as well as its own. The additional costs are just passed on to the other third party payer.

The state hasn't given UCSF freedom either. So it's not just the fault of UCSF. The school must establish a relationship with the state which gives it some freedom to operate cost effectively. Building laboratories at UCSF is much more expensive than building private labs. The management of money and space has largely been in the hands of amateurs. Not totally, because there are some very competent people at UCSF, but the bright lights aren't necessarily in control. The fact is that all the services are run by people who get paid much less than they could otherwise get if they were successful.

In addition, it is difficult to fire people at UCSF. By and large, the result is lack of competence. The university now might try to pay more money to its employees. However, standards for services have been lower than they need to be, so more money is paid to less qualified people, who want to keep their jobs. Despite all this, there is an immensely committed, hard working, and talented group at the core. The problem is at the upper layers of management.

I think it's the biggest problem in the university and in particular at UCSF. Budgets in larger universities can ebb and flow to some extent because the populations change and so on; they are more or less handled in different ways. It doesn't mean that they can't operate more effectively. They should and could and can. But UCSF is a special enterprise with budgets which have

¹ Dr. Rutter is a member of the Harvard Board of Overseers.

been determined over a shorter period of time, with no significant endowment, and health care costs are rising. Further, we have to suffer the consequences of the poor decisions that have been made. All of this puts pressure on freedom of operation and keeps people away from their fundamental responsibilities and precludes us from getting the most talented people.

Hughes: People aren't coming?

Rutter: Well, people are reluctant to take jobs at the high levels. Being head of Medicine is a tough job at UCSF, despite the fact that it's one of the best enterprises in the world. Part of the problem is one doesn't have space and resources to continue to grow and build. The recruitment realities are that we must accept 'caretakers'. You make internal appointments instead of bringing in external people who can foster change, or perhaps one doesn't get exactly the right person. One gets a person who will settle for what they have, realizing it's a challenge. I'm not downplaying the efforts of people like Floyd Rector who is doing his darnedest to make a good show of this but he is tremendously, seriously disadvantaged.

In fact, this is my only major complaint about UCSF. I believe that the powers that be in the school going back quite a long way were unrealistic about the future and about financial resources and the facilities that would be required for success. They didn't take those issues seriously enough and plan for the future.

Efforts to Develop the Basic Sciences: PIBS and the "Fifth School"

Hughes: Please comment on the Program in Biological Sciences [PIBS].

Rutter: I touched on the overall program in biological sciences, the notion of colonizing the departments with programs in biological sciences and the development of a cooperative program. Also, I mentioned the need to coalesce our programs with clinical programs, to essentially develop programs at the interface between basic sciences and clinical sciences. Both of those programs have been tremendously important because people coming into the academic medical departments usually need some kind of technological relationship, and in most places they are not given sufficient intellectual support, technical support, to build their programs. Quite frequently, they are quite severely disadvantaged, and it shows.

The PIBS program results from the cooperative joint appointment concept. We started it when I was chairman, but Bruce [Alberts] has dramatically extended it. Bruce and Mike Bishop and Zach Hall and many others--essentially the colonized group in these various departments--coalesced to make the Program in Biological Sciences what it is today.

Hughes: Did it have that name originally?

Rutter: No. The name was formalized when we began to seek money to support it. We got a big grant from the Markey Foundation. This is one of the things that Bruce Alberts has done so well. Bruce is interested in teaching and has further developed the basic science here remarkably. It was a cooperative enterprise with the rest of the departments. You couldn't possibly have a program in biological sciences when we first started because the level of science in different departments was so uneven. It would have simply been a disaster. We talked about it many, many times.

So the only thing we could do was to develop the science via recruiting, with the notion that eventually people would participate in a common graduate program. Before it was really a mosaic of different graduate programs, with very different standards and different quality of students. If the programs had been mixed at the beginning, it would have precluded us from becoming a premier institution because one would have had to deal with all the "dead wood" and mediocrity. We had a problem in the department itself during this transition, as I have mentioned.

But once one began colonizing the other departments, then the students spoke the same language and they began to take the same courses. The courses were then made large enough to cover the various fundamental interests and then the departments could give specialized courses as they chose.

Hughes: Ralph Kellogg mentioned to me the concept, which I think arose in the fifties, of a Fifth School.¹ Is what we're talking about somewhat related to that?

Rutter: Yes. The Fifth School was a [proposed] graduate school. It was always talked about as a way to make UCSF a true campus, where the Fifth School represented science. It was a strategy to get resources and people.

Hughes: But it never got off the ground?

¹ Telephone conversation, March 4, 1992.

Rutter: No.

Hughes: Is PIBS--

Rutter: In part, PIBS is the Fifth School. The idea of having the graduate school dean be a powerful figure on our campus, equivalent to the rest of the professional schools, was never possible because the resources haven't been abundant enough. Of course, the departments were too strong compared with the graduate school. We've never had a very strong graduate dean. The only way that could have happened would be essentially for the university and the state, maybe through private contributions, to really put some resources behind a Fifth School. That couldn't happen either because we had no space. So we were trapped.

The school had an unrealistic view about this just because of the space issue. It was totally impossible to develop a Fifth School without another campus. There was the notion that one might buffer the basic sciences from the stronger clinical departments. Maybe the basic sciences didn't have enough to say in comparison to the clinical departments in the running of the School. There was an argument for that.

Maybe things would have been better had we had a stronger graduate school dean. It's anybody's guess. The fact was and the fact still is that when the deans get together as a small group, we [the basic sciences] aren't represented powerfully. But I'm not sure that's the reason for our failure. I don't think it depends on background; it depends on attitude. If the chancellor and the rest of his crew are not attuned to running a close-hauled vessel, the vessel won't be close-hauled. That's all there is to it.

I think the Fifth School was a figment of the imagination of people who wanted to see UCSF develop into a full-fledged university ultimately having at least upper level undergraduate students. None of that would have been bad for UCSF. It could have been an interesting program. UCSF is a tremendous place for people to grow at a time when biological science is growing so rapidly, and interest in the human condition is so great. It would be a great opportunity for a focused university. I don't know of such a school in the country. It would be a nice experiment. However, no resources, no space, no practical vision, no commitment.



William Rutter at the UCSF news conference to announce the cloning in 1977 of the rat insulin gene, which is depicted behind him.



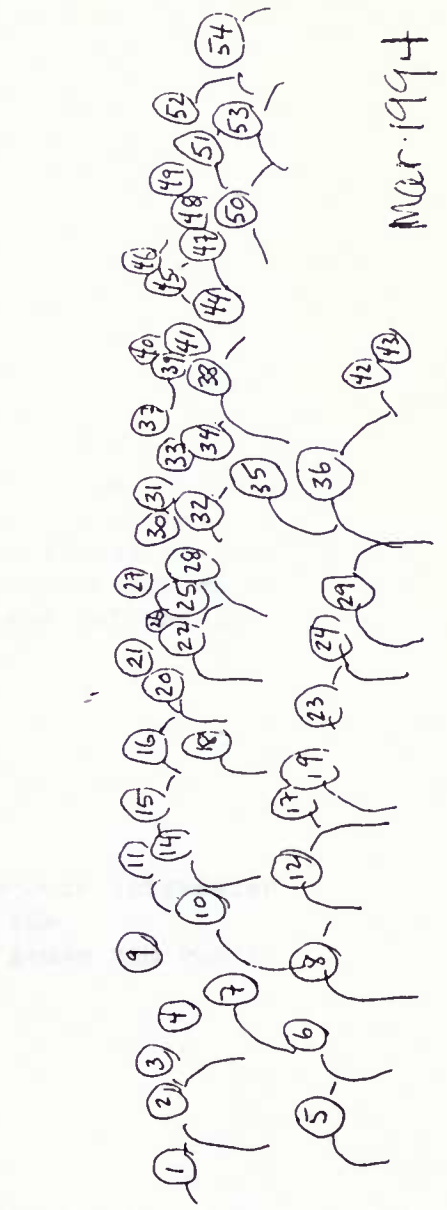
William Rutter and Orgad Laub looking at a gel.

Photograph © David Powers, 1984



Gathering for William Rutter's retirement from UCSF, March 1994.

Photograph courtesy of Leslie Spector



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|--------------------|--------------------|----------------------|
| 1. Mike Thaler | 20. Gary Van Nest | 38. Wing King |
| 2. John Chirgwin | 21. Larry Moss | 39. Lou DeGennaro |
| 3. Jeff Johnson | 22. Raymond Pictet | 40. Aubrey Thompson |
| 4. Gus Gustafson | 23. Leslie Spector | 41. Bob Rooder |
| 5. Meg Phillips | 24. Ben Yen | 42. Valerie Watt |
| 6. Giulia Kennedy | 25. Beulah Woodfin | 43. Baby Watt-Ingles |
| 7. Herb Leberherz | 26. Tom Sanders | 44. Yosuke Ebina |
| 8. Peter Hobart | 27. Mike German | 45. Sherwood Githens |
| 9. Michael Blamar | 28. David Standing | 46. Charly Craik |
| 10. Eric Clauser | 29. Yosef Shaul | 47. Bill Nikovits |
| 11. Ron Raines | 30. Mark Selby | 48. Rhoda Blostein |
| 12. Corey Largman | 31. Mickey Urdea | 49. Joel Gordon |
| 13. Laszlo Graf | 32. Jang Han | 50. Carmen Quinto |
| 14. Bernt Walther | 33. Patty Olson | 51. Kurt Jarnagin |
| 15. Ray MacDonald | 34. Chris Erwin | 52. Jens Nielsen |
| 16. David Overbach | 35. Jim Ou | 53. Anne Boulet |
| 17. Galvin Swift | 36. Jim Ingles | 54. Jennifer Meek |
| 19. Bill Rutter | | |

III RESEARCH IN THE MOLECULAR SCIENCES

[Interview 5: May 2, 1992] ##

Fundamental Scientific and Technology Developments in Genetics

Rutter: In the discussion of the scientific developments in genetics, which occurred in the early seventies both at UC and elsewhere, a major focus was on genetics and genetic transcription as well as translation, and how to deal quantitatively and specifically with a single gene or a composite set of genes as compared to other much more complex phenomenological attributes. For example, genetics at one level in animals had been more related to things like coat color, as in mice, or in the case of *Drosophila*, hair patterns and morphological characteristics. In humans, obviously, it was related to genetic disease with its consequences.

In each of those issues, most of the genetic phenomena were not single genetic traits but were complex genetic traits which in some cases had been resolved to a single genetic event but whose specific molecular basis had rarely been identified. So it was in simple organisms that the single gene-single protein relationship was delineated. It was in this context, therefore, that there was a general predilection to understand all phenomena in terms of single gene events, with the complexity that some proteins are composed of different polypeptide chains and therefore are multi-gene proteins. More recently, the concept has been refined in order to explain both the gene and its regulation.

Bacteriophage

Rutter: The main issue that was faced by those of us who were interested in higher organisms and specifically humans was the extraordinarily complex genome both in terms of genes and their

regulation. This issue, coupled with the difficulties in carrying out experiments had largely eliminated higher eukaryotes and humans as systems for studying fundamental mechanisms. Individuals had focused on simpler systems such as viruses, either viruses that affect bacteria (bacteriophage), or viruses that affect human beings or other animal species or plants. Because some of the viruses had a very small genome and had unique characteristics, they could be understood in great detail. But they still couldn't be studied in molecular detail until there were methods that were available for understanding the nucleic acid sequence and the patterns of translation and regulation. In the 1970s, great progress was made: the sequencing of proteins and the nucleic acids, sequencing of DNA, and biological systems were developed which would allow the facile use of genetic systems in mammalian or other cells.

One of the most interesting strategies for understanding genetic events in bacteria was to employ bacteriophage which could essentially infect bacteria and then destroy the bacteria to form plaques. The simplicity of the assay system made it possible to learn much about genetic regulation. The phage technologies then allowed fine-structure mapping of the phage, almost down to the nucleotide sequence, and the understanding of all the genes.

The great part about phage was that they could be used as infectious agents. Their physiology and biology were very well understood. Phage also were known to recombine with other phage so that they could pick up other pieces of genetic information. That genetic information could in turn be carried with the phage into microorganisms. Hence, artificial genetics was displayed and could be studied in such simple systems. Since recombination could occur between the genome of the bacterium and the genome of any compatible organism, one could also have transmissibility of infected genetic material into the genome of the organism. All these possibilities were anticipated, in principle.

In higher organisms the problem was more complex because obviously the genetic system was more complicated, and no simple experimental strategy existed. The viruses that were available were also more complicated. Plant viruses provided interesting information but were not so relevant to human cells.

Restriction Enzymes

Rutter: In all of these areas one of the crucial aspects was to be able to deal with the genetic material just as a chemical molecule. There

were basically two strategies for doing this. One of them derived from a biological approach to understand genetic restriction mechanisms in which one organism could eventually destroy another competing organism. It was found that this was due to the presence of enzymes called restriction endonucleases, which essentially attack the foreign genetic material, while the host genetic material was protected by some modification. Restriction endonucleases were considered at first to be just a curiosity, but they became a real tool in being able to characterize DNA and obtain pieces of DNA, by virtue of their great specificity.

Clearly, the recognition that the sequence of nucleic acids was monotonous--it was comprised of four building blocks as opposed to the twenty elements in proteins--also provided a challenge in trying to understand the biological meaning in sequence just because of the lower degree of complexity of the chemical structure. Restriction endonucleases cleaved only at specific target sites that were comprised of several nucleotides.

Recombinant DNA Technology

Rutter: Herbert Boyer had come to UCSF from a laboratory at Yale which had focused on restriction endonucleases. One of his major interests was to study the specificity of one of the restriction endonucleases, EcoRI, and to establish the molecular mechanism of its extraordinary specificity. As the name implies, EcoRI was derived from E. coli.

During this time, it became evident to Herb and also to others that restriction endonucleases could be used to clip pieces of DNA but also to reassort DNA. Because some of the restriction enzymes cut in such a way as to leave overlapping, single-stranded ends, these could combine with other nucleotide sequences which had a complementary single-stranded region. They were termed "sticky ends" because they provided a way of joining DNA. As the enzymes which were involved in nucleic acid metabolism, synthesis breakdown and repair, and the biology of the system became better known, these could be used to covalently join such ends to form a molecule.

This ability to be able to clip a piece of DNA and join the pieces back to the same segment led to the obvious alternative to link with another piece whose sequences were divergent from the original piece. So one could produce a chimera in which two foreign fragments were joined by virtue of a single common sequence. This was a marvelous piece of biology and genetics and

chemistry because it was the first means by which you could move around pieces of a polymer which was impossibly long and for which there was no other known mechanism for selectively cleaving it in the laboratory.

Hughes: A Stanford group had previously joined DNA from different sources without using sticky ends.¹

Rutter: Yes. There were ligases that joined blunt ends.

The main point that I'm trying to make here is that the enzymes that were available allowed joining. Obviously, some of the restriction enzymes cleave with blunt ends. Different enzymes can join either blunt ends or sticky ends. Thus there were several different ways of cutting and piecing pieces of DNA in a more or less specific fashion. The techniques also provided a way to identify pieces of DNA by common restriction fragments and lengths; identical molecules obviously had to have the same sequences at the same distance. In other molecules, they had to have some sequence identity to exhibit that phenomenon. If one could carry out the same cleavage reactions with several different restriction enzymes, then the cleavage patterns provided a quite persuasive argument for identity or for difference. This was a means to characterize even complex DNA molecules.

Thus these peculiar enzymes of certain organisms turned out to be exceedingly useful in characterizing all DNA and some RNA molecules. Very rapidly labs became focused on getting a large repertoire of restriction enzymes in order to characterize DNA.

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Rutter: The restriction enzyme approach didn't give us ultimate structural information but did provide us a way to understand structure by virtue of the pieces of DNA which were incorporated in the structure. Because the combinations were defined by sequence most of the time, one could join two foreign segments. This was the first major development in recombinant technology.

¹ For accounts of recombinant DNA research at Stanford, see the oral histories with Paul Berg, Ph.D., Stanley Cohen, Ph.D., and Arthur Kornberg, M.D. in The Bancroft Library Series.

Networking in Science

Rutter: One possibility, and we talked about this, was to set up a lab to purify the restriction enzymes, to develop them ourselves, this being necessary for our own research, essentially giving us a competitive advantage over other labs. But we did it by networking instead of setting up a devoted lab.

Hughes: Talk a little about the networking.

Rutter: Well, as today, science at that time was carried out by a global network of small labs. The nodes are made up by individuals who have common interests and whose interests complement each other, either on an intellectual level or a practical level. The purpose of scientific meetings is to develop such a network and intersect with it, so that one can anticipate what everybody else is doing and also decide how one can best complement or add something unique that others aren't thinking about.

In this particular area, restriction enzymes were discovered in the laboratory of Werner Arber in Switzerland, but there were several people from the United States in his laboratory who continued to work in the field and formed a network. They collaborated with lots of other people who were studying the restriction phenomenon to develop enzymes of various sorts. Pretty soon individuals would exchange restriction enzymes. The net result is that everybody benefited because they had a larger repertoire of such enzymes.

Hughes: It was a tit for tat arrangement.

Rutter: Yes indeed, in part. Obviously the network operates best when you can provide a service in return for something they provide. But the network also provides reagents either freely or, more often, on a collaborative basis. If the collaboration is more intense than just reagent exchange, then it usually extends to joint authorship on a publication.

That's how the great laboratories in Geneva and Cambridge and in various places in the United States would establish themselves. The groups were large enough that they usually could provide reagents and special expertise to each other. In a rapidly developing field where special reagents are needed and the technology is complex, no small lab can be competitive. Thus a department like ours, with a certain scientific concentration, begins to have a power unrelated to its size, by accumulating technologies and reagents and expertise.

Hughes: Can one deduce that because of these networks there were research collaborations that perhaps otherwise might not have occurred?

Rutter: Absolutely. In order to establish the network, you had to first of all have a way in.

Hughes: Which sometimes was simply something to offer.

Rutter: Or somebody knew that one was a pretty good guy and worth sending a reagent to because you wouldn't spill it all over the floor. [laughter] Or you were a clean enough thinker that it would be useful, because obviously these reagents had great value. And/or that somebody else had another reagent from another lab in the vicinity. Networks are established in a variety of ways but they all depend in the end on personal relationships.

Hughes: What about protocol? If you received a ligase from one lab and a third lab came in and asked you for it, could you give it away?

Rutter: No. Now there is a formal agreement that one signs with respect to others' reagents that one won't pass them on without express permission.¹

Hughes: But earlier, it was a gentlemen's agreement?

Rutter: In those days it was a gentlemen's agreement. It wouldn't be acceptable protocol for me to transfer your reagent without your approval, or to become part of another collaboration which depended solely on your reagent. So the strengths of the research effort at UCSF were in part based on the fact that we had developed a fine network with various scientists so that we could access rapidly the newly developed technology, and prospectively return the favor.

Sequencing Techniques

Rutter: The second major achievement was the development of methods for sequencing. How does one determine the sequence of monotonous combinations of four nucleotides? Obviously, restriction enzymes allowed one to pare down the DNA to manageable pieces. But then one had to have a way of determining the order of the units. There were two strategies that were developed by two great

¹ Rutter's correspondence at UCSF Library documents an increasing formality in reagent exchange, from the 1970s into the early 1990s.

scientists: one at Harvard, Wally Gilbert, and the other at Cambridge, Fred Sanger. Wally's method, was a chemical method based on modification and cleavage and was related to the stability of bonds that were altered by chemical derivatization. In the case of Fred Sanger's, it was--

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Rutter: --a separate mechanism involving synthesis, based on formation of a copy strand. The Sanger method turned out in the end to be the more facile and is almost universally employed today. But the Gilbert method was tremendously important in the early days. Suffice it to say that the labs that had first the Gilbert method and secondly the Sanger method early on could sequence DNA much more effectively than others.

Hughes: Was that the case in your lab?

Rutter: This was the case in the department and as a result in my lab. This capability was largely due to Howard Goodman who became a key technical resource and collaborator.

Hughes: This strategy was aimed at the gene for insulin?

Rutter: No. The insulin gene came later. These were general strategies that allowed us to deal with DNA molecules, ones that led to the development of the cloning process itself.

Hughes: So you were not thinking of the insulin gene yet.

Rutter: No, the insulin gene work came several years later.¹

Hybridization Techniques

Rutter: The third approach was hybridization using the fundamental properties of DNA to form complementary duplexes. The combination of two strands was dependent on complementary sequence (adenine:thymine and guanine:cytosine) and on concentration. Clearly, if the two complementary strands were in low concentrations and took a long time to find themselves, the rate of hybridization would be very slow. But if they were present in high concentrations, they would immediately click together. So,

¹ The Rutter-Goodman team published its research on cloning the rat gene for insulin in 1977.

the abundance of a species could be characterized by the rate of hybridization.

A whole area of research sprang up around this method. For example, if one purified the messenger RNA from the red cell, a complement to hemoglobin (cDNA) would immediately hybridize to the hemoglobin mRNA. In this way one could purify the hemoglobin cDNA from the rest of the material which was non-hybridized. This allowed one to isolate pieces of DNA that were highly enriched. Thus by choosing a cell that specialized in expressing a single gene, one could isolate the mRNA or the cDNA. Making a cDNA required an enzyme which was able to make a copy.

Retroviruses had such an enzyme, a reverse transcriptase. Mike Bishop worked on retroviruses which had this capability of producing the reverse strand to make a double-stranded structure (hence the term retroviruses). By forming cDNAs and carrying out sequential hybridization, one could enrich the most highly concentrated species. This process allowed one to think of obtaining a cDNA of insulin because the islet beta cell is a little bit like the red cell in that it produces largely [one kind of protein,] insulin. If one could get good beta cell preparations from the islets of Langerhans, you could purify the RNA, form cDNAs, and end up getting relatively enriched species.

Research in the Rutter Laboratory in the 1970s

Transcription Enzymes and Pancreatic Differentiation

Rutter: In the early 1970s, our lab concentrated on two things. One was the enzymes that transcribe DNA to RNA to make messenger RNA. What were the regulatory events? There were three RNA polymerases and there were ways to inhibit or modulate the activity of each one. Only one of the three enzymes really made message, polymerase II. The other two were involved in making the RNAs that are associated with making ribosomal RNA, that is, used in translation. Polymerase III is involved in making small RNAs like tRNAs [transfer RNAs] and other accessory RNAs. The toxin of a mushroom, Amanita phalloides specifically inhibits one of these enzymes intensively, the other one less intensively, so that one could assay the relative concentrations of the enzymes and control the production of messengers or small RNAs, as opposed to ribosomal RNA.

Secondly, we were analyzing the differentiation of the pancreas. We had chosen the pancreas because it was selectively differentiated to produce high levels of digestive enzymes as well as the hormones insulin, glucagon, somatostatin, and so on. So the differentiation process could be characterized by analyzing the expression and also by the use of hybridization techniques. We attracted Brian McCarthy who was an expert on hybridization and had characterized a number of genes that were expressed in many different organs and tissues by virtue of hybridization rates.

Cloning Methodologies

Rutter: The several different methodologies required for cloning were all in place, that is, one could obtain RNA enriched in one or several mRNAs. One could reverse transcribe the mRNA to form the cDNA. One could clip the DNA or cDNA and form chimeras. One could carry out structure analysis on small pieces of DNA via either the Gilbert or the Sanger strategies. One could also carry out transfection into plasmids, viruses or phage. Phage turned out to be more useful because of this tremendous technology that had been associated with phage biology and our ability to pick plaques and so on.

The first five years after we came to San Francisco was a time of refinement of these strategies, both here and elsewhere. Our orientation to higher organisms and humans began to be more serious and practical.

The Cohen-Boyer Experiments

Rutter: In 1973 or 1974, Herb Boyer and Stanley Cohen got together at a scientific gathering in Hawaii and started describing what could be done with chimeras. The first experiments simply demonstrated that cloning of pieces of ribosomal RNA could be performed.

Hughes: Those experiments were largely at Stanford?

Rutter: No, not really. If you're talking about the initial experiments by the group at Stanford in Dale Kaiser's and Paul Berg's labs, these simply demonstrated the formation of a chimera between a given piece of DNA and another piece of DNA. The chimera obtained was not involved in a cloning experiment.

The Cohen and Boyer experiments were really directed with the express purpose that one could produce a foreign DNA via the cloning methodology. This was a very powerful and different concept. It was another significant advance to use chimeras in a functional way, i.e., to have genetic control over the expression of a piece of foreign DNA. Those experiments were done in Cohen's lab. But Herb's lab provided the crucial components of the experiment.

Hughes: Do you care to say who was doing what?

Rutter: You should get the story direct from Herb.¹

The Cohen-Boyer experiments demonstrating cloning caused an avalanche of interest because of the obvious possibilities. This was discussed in one of our departmental gatherings in a little Biochemistry and Biophysics meeting room next to my office on the ninth floor where the Biochemistry office now is. The room had gray chairs and dull green walls, however the discussions were lively and frequently exhilarating.

Hughes: This was your lab group?

Rutter: No, this was the whole department.

Herb Boyer described setting up the experiment and told us immediately about the concept. We discussed the various possible results and the new experiments that could be done. Which genes should he work on?

Hughes: Was he in the department?

Rutter: Originally, he was in the Department of Microbiology. But we included him and also Bishop and the other good guys from that group almost immediately [in Biochemistry discussions]. They became actual members of the department, but somewhat later. We had a core group within the department that centered on molecular genetics and human biology. People interested in this field who were not formally in the department were still in the core, just because of their interest.

Hughes: So that was Boyer.

¹See the oral histories with Boyer and Cohen in The Bancroft Library Series.

Rutter: Boyer came into the department in 1975 and so did Mike Bishop and Harold Varmus.

Hughes: Was anybody worrying about expression at that particular moment?

Rutter: Yes, expression systems were being developed at the same time, but largely with bacteria. The first cloning was to focus on the DNA itself. Of course, once you had the DNA, then the next challenge was to express it and measure the protein. So it was expression screening of cloning. The first way to identify a clone is by the DNA and the second way is by the protein which the DNA encodes.

Decision to Clone the Rat Gene for Insulin

Rutter: When the cloning methods were being developed in '73-'74, it became possible to envision for the first time cloning a gene that we were interested in. Of course, the insulin gene was the most attractive. The insulin gene had the virtue of being small, not as small as somatostatin but it turns out that the gene size is not that much different. The fact that insulin gene was small, that it was expressed in a single cell type, and that you could develop methods for isolating it made it very attractive. We were also studying gene expression of the exocrine pancreas, genes encoding enzymes that digest proteins and nucleic acids, DNA and RNA. But these genes were comparatively large, and were less interesting at the outset.

Hughes: These are all scientific reasons for trying to clone the insulin gene. Were there nonscientific reasons?

Rutter: At that time, I had no commercial interests. I wasn't even sure that there was a commercial use for human insulin. As far as I knew, diabetics got along quite well on beef and pork insulin. So the idea of cloning the insulin gene just to provide another method for synthesis of insulin wasn't a powerful incentive to me.

Pig insulin is every bit as good as human insulin. The combination of beef or beef and pork insulin does a very good job. Those at Eli Lilly believed that the down side of using a recombinant process to produce human insulin might have been greater than the upside of having a human protein. It was only the endocrinologists and maybe ultimately the patients who preferred to use human insulin rather than pig or cow insulin. There are very few cases where one gets a severe and disabling immunological response to animal insulin and the view that this would represent a "cheaper" source of insulin was a fiction.

However, as I learned later, there was a danger of short supply. The number of diabetics was increasing to a point that the beef and pork industries could not meet the demand.

Hughes: You didn't talk in 1973 and '74 of producing human insulin for commercial purposes? That talk came later?

Rutter: We wanted the insulin gene in order to study its regulation. Eventually perhaps we wanted it to develop a genetic approach to insulin expression in diabetes, perhaps to bypass the production of insulin in the beta cell. Initially it was a biological strategy with no real connection with commercial interests. However, it did also allow the development of systems for the production of insulin and a study of the processes involved.

Our lab was involved in this development. It focused at one level on the islets, glucagon and insulin and somatostatin. But of those hormones, insulin was the most interesting. We wrote up a grant application at that time to try to get funds to clone the insulin gene.

Hughes: To whom?

Rutter: To the NIH. And it was received with great interest, but not approved finally.

Hughes: Do you know why?

Rutter: Yes. We had a site visit. We were given several reasons why. We hadn't done any cloning before. Our own work had been focused mostly on transcription and on development but not on this kind of science. So we were experienced and productive in one field of science, but essentially prohibited from using dramatic breakthroughs to expand knowledge in our field. Other scientists might have been interested in the subject. The view was that this was probably an impossible venture and even if it were to be done, we weren't the ones who could accomplish it.

Hughes: Was Boyer supposed to be part of this research?

Rutter: No. The proposal came from my lab itself. Shortly after the initial cloning experiments, Boyer became interested in a number of different possible cloning targets. We were hoping that he might become involved in a cooperative project, but this did not work out. The formation of Genentech [1976] changed all that.

Gordon M. Tomkins ##

Role in the Department

Rutter: During that crucial period of time, in 1975 Gordon Tomkins died. I'll recount to you a little bit about Gordon's death because it had such a tremendous impact on each of us as individuals, on the department, and on the school too.

I told you before what a truly marvelous person Gordon was, and how he contributed to the spirit and overall attitude of the institution. Things were lively; we used to have parties in which Gordon and colleagues provided the music. He was very inquisitive, very friendly, and very collaborative, without in any way being threatening. He contributed in a major way to the marvelous environment we had. He helped to balance, for me and for many others in the school, the intensity of our efforts to make UCSF better and of course keep our labs functioning. Gordon always had very good relations with clinical departments because he himself was clinically trained and was well known by the clinicians. He also had a marvelous way of presenting information--sophisticated conceptualization coupled with humor.

At the same time, Gordon was frequently criticized by some scientists outside UCSF. His tendency was not to drive science to the level of detail that scientists frequently like but rather to deal with the important new conceptual advances, and of course he was charming and human. To some this meant a lack of seriousness. Gordon always led the intellectual foray but he didn't always finish the argument, so much of his work was controversial. He was interested primarily in hormone action, but hormone action translated into regulatory mechanisms at the most fundamental level, including control of gene expression.

Several excellent scientists came from his laboratory. He gathered good people like the Pied Piper--Keith Yamamoto,¹ Pat O'Farrell, John Baxter, David Martin. Some of UCSF's best people came from Gordon's lab. Gordon held a special attraction for those people with medical training that wanted to do biology. He also managed to get a lot of good postdocs who were interested in biology and who came from other disciplines, such as physics or chemistry.

¹ For Yamamoto's views on Tomkins, see his oral history in the UCSF Biotechnology Series.

Tomkins' Illness and Death¹

Rutter: Unbeknownst to me was the fact that Gordon had problems with his balance and with hearing. It turned out he had developed a tumor on one of his auditory nerves. It was obvious to him that it would get progressively worse. He used to experience tinnitus and began to lose his hearing and balance. He was also acrophobic and perhaps his lack of balance exaggerated this condition.

After several months of exploring various alternatives, he told me that he had discovered a surgeon in New York, at Mt. Sinai [Medical Center], who had developed a new, space-age surgical technique that allowed him the prospect of total removal of the tumor cell by cell, without damaging the nerves and therefore without losing either his hearing or his touch! Previously, the surgical strategy had been that you went directly in the ear, in which case the tumor could be removed but one lost hearing in that ear. Alternatively, a surgeon could go through the mastoid bone and upwards in which case one lost most of one's touch as well as some hearing. The new approach was to use microsurgery (this was one of the first microsurgical techniques) and pick out the tumor cell by cell. This is an extremely laborious procedure, but apparently these tumors are sufficiently constrained to a certain area so the probability of success was relatively high.

Gordon talked to lots of people about this. He had many good medical friends both at the NIH and Harvard where he trained, and at every major medical center. Thus he had obtained the best advice. He finally told me one day, "This is, after all, a minor operation but you never can tell what happens with operations like this." So we talked about his preparation for the financial well-being of his family and so on.

It was done in such a light-hearted way that I never really considered the risk any more serious than the possibility that he could lose his hearing. And nobody else did. Except perhaps Charlie Wilson, a great neurosurgeon at UCSF. Charlie advised, "Don't go with this guy. This procedure is absolutely too avant-garde. I can do a better job for you here." Gordon went for the high-tech approach, which was typical of him. Finally Millicent [Tomkins] and he went back to New York. She stayed in the apartment of the mother of some friends at the NIH. We anxiously awaited the word: they reported that the operation was a tremendous success. He had to sit up in a space suit for nine or ten hours, and the microsurgical operation was carried out with the aid of television cameras.

¹For more on the repercussions of Tomkins' death, see the oral history in the UCSF Biotechnology Series with Keith R. Yamamoto, who at the time was a postdoctoral student in Tomkins' laboratory.

So the operation was successful but the patient died. I've forgotten the name of the major surgeon, but the second surgeon was named Sajdev. At first we were totally elated; so was the surgeon. He said, "This was a perfect operation. We have removed every single tumor cell." He then got on a plane to attend an important meeting. As it turned out, Gordon developed a dissecting hematoma at the brainstem. Over time, the blood separated the brain and its surrounding membrane from the skull and built up enough pressure to make the brainstem dysfunctional. There was no way to tell that was happening. The surgeon had implanted little steel rods to monitor with x-rays to take care of this situation. The concept was if a hematoma developed then the position of the rods would change. They didn't. We got progressively more worried when he hadn't come out of the coma after the first, second, and third day. I flew back to New York.

Hughes: The surgeon, I hope, had come back from the meeting?

Rutter: No, the surgeon didn't come back until it was evident that something disastrous had happened. Sajdev was also a marvelous surgeon but it was an unusual situation where they had no real experience. Of course they operated again to remove the hematoma but the physical damage had already been done. Gordon never gained consciousness but was alive for several months. When it became clear that there was no possibility of recovery, they let him die.

That was a tremendously difficult period of time of course for his family but also for us. It was a fantastically busy time. Major changes were occurring at UCSF, concerning the emergence of recombinant DNA and biotechnology. I had to take over Gordon's lab. I also had my own lab. The general management of the science was in good shape but management of the lab in transition was difficult. It also was a difficult time for me personally. I finally decided that Bonnie and I should divorce.

Aside from the personal tragedy, the net result of Gordon's death was that the department and the school lost a major international figure as well as a major cohesive force. Gordon played a really important role in building the department itself, for sure. But by that time, I was in very secure control of the administration and the department function. There was never an issue of the department unravelling, although some people might have chosen to leave at that time. It was just a matter of getting it all done and reasserting our developmental trajectory.

Pulling people together would have been easier if we had had more senior scientists in the department or if the political issues had been less severe.

The Asilomar Conference on Recombinant DNA, February 1975 ##

Rutter: After the cloning experiments, scientists and non-scientists became intensely interested in the subject. People realized its possible impact in the 1975 to 1976 time frame, and the whole scientific community became involved in two major issues. One was the possible danger and control of recombinant DNA research, hence the Asilomar meeting. The other was in the prospective utility of this technology, hence the beginning of Genentech and the biotechnology business. Both of those issues affected our department positively and negatively.

Hughes: Did you go to the Asilomar meeting?

Rutter: I did not go. Gordon, Herb, Howard Goodman, and several other people in the department went.¹ I have to admit that I was fundamentally against such a public meeting. I felt that the conference brought into the public arena issues which should have been allowed to mature more, rather than to hold such an open meeting subject to the flamboyant players. The rather extreme points of view would gather a lot of attention, particularly from the press.

Hughes: Views on the opposing side?

Rutter: Yes, on the opposing side. Possible dangers had to be considered. I thought these would be overly emphasized and they were.

Hughes: Why did you anticipate that?

Rutter: I thought it was obvious that in our environment, dangers are always emphasized over justifiable risks. Consider the Delaney amendment, which still plagues the development of anticancer drugs, or in another field, the overreaction to radioactivity, per se. The specter of danger was ever expanding.

Hughes: You're saying that well before Asilomar, there were discussions amongst scientists of the potential dangers of recombinant DNA research?

Rutter: Among individual scientists, yes. A number of these people got quite exercised about these dangers. Many of the people who were exercised about the dangers also didn't know much about the

¹ Michael Bishop also attended, but not Howard Goodman. ("List of Participants for Asilomar," Paul Berg correspondence. SC 358, accn. 90-020, box 1, folder: memos 1975.)

details. I also didn't know much about the details, but I thought that one needed to coolly analyze the reality associated with recombinant research; such a meeting was not set up to carefully study the dangers and then, later on, determine when and where restrictions should apply.

Hughes: Had you tried to get a more reasoned approach? The Asilomar meeting had been planned for some time.

Rutter: It clearly was organized over a period of time. There were people who were talking about the risks. We hadn't contributed to the analysis but, unfortunately, neither had anybody else.

Hughes: Analysis of the dangers, you mean?

Rutter: Yes, a careful analysis of exactly what the issues were, of what the prospective dangers were.

Hughes: From a theoretical standpoint.

Rutter: From a theoretical and also from an empirical standpoint.

Hughes: Wasn't the NIH Recombinant DNA Advisory Committee [RAC] investigating the potential or actual threat of recombinant DNA research?

Rutter: No. They hadn't been established at that time.¹ Eventually, the committee did not assess the dangers per se. They monitored research within the context of guidelines. It was a quasi-legal organization. The RAC committee both established guidelines and administered them. So it was both a legislative and an executive body. But it had no funds to really look into the dangers per se, so it was a question of drawing only from the literature and from existent knowledge. But of course, the NIH was very interested in the "dangers" of DNA research. Thus a number of scientists obtained grants that focused on assessing and ameliorating the dangers.

The Asilomar conference was set up to deal prospectively with unknown issues, but in a conservative way. I did not and do not question the motives of the organizers, but I objected to the format. Our department didn't present an alternative. In fact, it would have been totally counterproductive to do so.

¹ Recombinant DNA Advisory Committee [RAC] met for the first time shortly after the February 1975 Asilomar meeting.

A number of people from the department participated in the Asilomar discussions. Obviously, in hindsight I should have gone. The moratorium also became a political issue. Who prescribed the rules? There were committees established which were more or less ad hoc. There was a lively debate on whether there should be a formal regulatory body established by Congress that would essentially administer regulations as laws. I and many others were dead set against having laws operative in a field where we had no information. It was a totally artificial circumstance. But the politics of using this technology became a fact of life.

The Birth of the Biotechnology Industry

Rutter: The other fact of life was the beginning of the commercial realization of the commercial power of this technology. The initial experiments clearly opened an almost limitless horizon. At one end of the commercial scale people were saying, let's be practical, what are you going to do with recombinant DNA technology? But there were others who saw limitless potential, and with it, immense wealth.

The experience of the computer and the chip technology business generated similar notions of remarkable and rapid progress. The enormous wealth created by that business encouraged the venture capitalists to focus on new technologies. Before that time much venture capital had been devoted to things as mundane as oil drilling, where the probability of drilling a productive oil well was pretty well known in a given field. While the risk was high, the rewards for success were relatively enormous. The Silicon Valley companies were based on rational approaches. The question was not so much could it happen but who would do it first and best. These investors realized the rewards could be great and with less risk.

Genentech

Rutter: Kleiner and Perkins [a venture capital firm] had come out of the Silicon Valley and became wealthy and set up this vehicle to use their wealth to start other enterprises. Largely that company continued to develop Silicon Valley, but then Bob Swanson joined them from Citibank [Venture Capital Ltd.]. He was a young executive for Citibank, a biologist trained at MIT who started

with Kleiner and Perkins with the explicit intention to do something in biology.¹

When the proposal to start a biotechnology company was made to Herb Boyer by Bob Swanson, Herb was immediately drawn into it. They decided to make it a limited relationship. They didn't want to share the responsibility or share the wealth or whatever. Herb and I have never had a totally frank conversation on this subject till this day. What did happen was that Boyer began to focus his interests very specifically on how to use this technology. If you wanted to synthesize a useful protein you either had to isolate the gene or mRNA, or synthesize the gene.

The chemistry procedures were just being developed for synthesizing oligonucleotides. They were tedious. One couldn't synthesize long genes. Insulin was relatively short, but was still too long, roughly a hundred amino acids (=300 nucleotides), a pretty big synthetic chore. Boyer and Swanson became interested in developing synthetic means--the fifth technology that was brought to bear in this sophisticated science. Early on they had decided that, although they might isolate genes, it would be tedious. The amino acid sequences of many proteins were also already known, so probably the best way was to synthesize the cDNA. Keiichi Itakura from City of Hope [Medical Center] was one of the best chemists for synthesizing oligonucleotides. He was dedicated. He had a good group of focused individuals who could work on this. He collaborated with a geneticist at City of Hope and those two scientists became quite a good team.

Hughes: Who was the geneticist?

Rutter: Arthur Riggs. These two people and Herb began to collaborate and they were drawn into the Genentech organization in 1976, 1977. At that time, then, many of our interests began to fractionate because of the commercial orientation of a key part of our environment.

Problems at UCSF Associated with Commercialization

Hughes: What were you thinking at that time about the commercialization that was occurring right in your own department?

¹ For more on Robert Swanson and the formation of Genentech, see his oral history in The Bancroft Library Series. Swanson majored in organic chemistry at MIT.

Rutter: Maybe it's a better idea to talk about what we were thinking.

Hughes: The "we" is the department?

Rutter: Yes, and of course I will say what I was thinking about.

There were members of the department who were totally opposed to any commercial interests. Keith Yamamoto was the most rigorous opponent,¹ and others felt similarly, for example, Christine Guthrie.

Hughes: What were their arguments?

Rutter: That whenever a commercial issue gets involved, it changes the quality of the lab. It brings in strong extraneous motives which aren't compatible with the purposes of the university. Ostensibly, occlusion of experimental results may happen and so on. But scientific competitiveness exists everywhere and people do hide information whether or not commercial interests are involved.

But other influences crept in. As the individual labs became progressively more well known and distinguished, friction between individuals began to mount and cooperation, which has always been high (and still is high), took on a more acquisitive tone. People began to negotiate outcomes and rewards prior to the experimental results.

In the early days, Howard Goodman collaborated with many in the department. He was a very valuable member, both in his own right as a scientist and as a collaborator because he provided technologies. More than others in the department, he focused on the methodologies. He loved to develop methodologies, not that he was uninterested in fundamental mechanisms but he was more unique technically and was a good collaborator to many. He collaborated with Herb Boyer, John Baxter, Mike Bishop, Harold Varmus, and of course with us. In all these labs, one or another individual wished to pursue an aspect of a problem using recombinant technology, but the lab didn't want to become converted to a recombinant lab per se. They had their problems to solve.

So we became committed to the insulin project. Despite the fact that our grant application wasn't approved, we didn't allow that to stop us from going ahead. [laughter]

¹ For Yamamoto's views on this and other subjects, see his oral history in the UCSF Biotechnology Series.

Hughes: There was a problem with money, was there not?

Rutter: Always a problem with money, for sure. We could have mounted a much better program, a specific program, if we had gotten funding for it. Frankly, we indirectly used resources from other research grants; we had some money in the department provided by the School that could be used to supplement research grants. This illustrates why entrepreneurial capital was so important to our development. It was available not just in my case but for everybody in the department. We had to decide, one, how much were we going to use our resources to push this technology and, two, whether commercial work could be done.

I told you about the division in the department with respect to Genentech. At the time Genentech was formed [1976], I had no personal commercial interests, nor a particular interest in Genentech itself, although I encouraged Herb to include people of the department at some level. I think he said, basically, let's do this later. I felt that if he had included departments, either as individuals or as groups (I didn't care which), that there would have been much less concern [at UCSF about Genentech]. The aspect of sharing at whatever level would simply diffuse the matter. However this didn't happen. Despite that, I favored the Genentech organization and its temporary use of UC facilities on the grounds that it ought to be done. This was another way to get things accomplished.

Hughes: The research ought to be done.

Rutter: Yes, and the commercialization, if warranted. I felt that it was in the best interests of the University and the department to support this program, not to drive it away or delay it. So I tried very seriously to contain this early program within the bounds of the university. On the other hand, I also quite aggressively tried to have the university share in the rewards of such sponsored research. Overall, I was more concerned with the development of the research program rather than the commercialization process itself.

Hughes: How successful were you in getting rewards for the university?

Rutter: The university at that time was totally amateurish about dealing with intellectual property. It had a single woman in the patent office. Her name was Josephine Opalka. She didn't have professional training as a patent officer or an attorney. However, Jo Opalka was a committed individual and not a bureaucrat. From her background as secretary, she did a super job. But she was no match for people like this. The university

had no experience and no governing principles [in patenting procedures].

Furthermore, the university made agreements without contacting me as head of the department with respect to their financial basis. It was their practice to keep financial matters away from the administrative officers, perhaps because they didn't want us to try to get any of the funds (which would undoubtedly have been my intention). So it was only years later that I learned that the royalty rate that they negotiated with Genentech was so outrageously low. Here they were providing facilities, providing a jump start for this company, essentially saving it lots of money and time, for virtually nothing in return.

Hughes: Providing the personnel, too.

Rutter: The university is in the business of training personnel for other groups. Here I see it is no different from any other industry. We don't tax the industry for the personnel trained by the university. This is one of the benefits of corporate taxes. So the trained personnel who went to Genentech were just fulfilling a professional pathway.

However, there is no doubt Genentech had a favored position. It was the facilities and the availability of unpublished technology and the general experience of the department that was available to Genentech, a tremendous advantage. I don't believe either Bob nor Herb saw that issue clearly. It's a subject that I've always totally disagreed with them about.

There were others in the department that had truly contributed to work that was carried out by Genentech, for example, on gene expression and the future interests of biotechnology. Pat O'Farrell, David Gelfand, Barry Polisky, and Robert Bishop demonstrated expression of foreign proteins in bacteria and yeast.

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Rutter: Nevertheless, I argued strongly that Herb and his lab and whoever else wanted to collaborate with Genentech should be able to do that, at least during a period of transition. The university should get its value from it and everybody should keep cool. The fact was that commercialization was going to happen anyway so instead of denigrating it and isolating it, I felt all could benefit.

Hughes: Were you able to quell the dissension?

Rutter: Only partially. There was a fair amount of bitterness which resulted from this which extended for several years, I have to say.

Dealing as Chairman with Departmental Issues

Hughes: How were you trying to handle these complex issues?

Rutter: By a lot of dialogue. We had several ways of dealing with general issues facing the department. Although we never formally voted after debating the pros and cons of the issues, I always discussed matters with the key individuals so I knew their opinions and the reasoning behind them. So I never brought up an issue for final action until I knew that the group was in agreement with the direction I wanted to go. This principle kept people informed and involved without forcing confrontation of alternative views in a public forum. This had the effect of creating consensus, rather than emphasizing divergence of opinion. Using this general principle, we never brought the Genentech arrangement [in the department] to a vote. We handled it quietly. Of course, everybody knew about it. Some were more skeptical than others and certainly some individuals were negative, but a public debate and a formal vote would have split the department and sooner or later would have become public knowledge. This would have alienated Herb Boyer and colleagues. The fact was that many didn't know where they stood, and likely their opinions would change. One shouldn't make rules prematurely, when all the information is not available.

Hughes: How did members of the department feel about deciding issues out of court?

Rutter: I'm sure that there were differences of opinion. If you ask people about how I operated, you would find people who thought that I was maybe a little too strong-willed and single-minded in the way I acted. But I also think that many people supported my leadership style. I believe that if you ask people today that they would say it was basically a good time. That doesn't mean that people agreed with everything I did by any means. With respect to Genentech's role at UCSF, it would have been close to a fifty-fifty situation.

Hughes: Did that ratio shift as time went on?

Rutter: Yes it did, but it took ten years.

Herb became a truly controversial figure because of the intensity of feelings generated about the commercial connection and the profit motive itself. I believe in a family one doesn't harp on the differences and the controversies; one emphasizes the similarities and shared values if you want to stay together. It's the same situation in a collegial group. One must tolerate different views and try to build some kind of common understanding and respect for individual goals and contributions.

The spirit of the sixties was not ecumenical but confrontational and several of the people who were at UCSF were definitely out of the sixties. They wanted to march on City Hall, City Hall happened to be on the ninth floor.¹ [laughter]

The Safety Issue

Rutter: Then, exploring the broad areas the technology and controlling the technology via the RAC [Recombinant DNA Advisory Committee] guidelines, and eventually getting into the business ourselves became issues.

Hughes: How much were the guidelines interfering with the momentum of research?

Rutter: Early on, not at all, because the guidelines were informal and considered sensible. There was a lot of talk about them but they were not promulgated in a way that interfered with basic research. We had intense meetings of the NIH committee, trying to formulate guidelines, which were changing all the time. [At first] they were not published and they were transmitted by word of mouth and telephone.² All the key players knew about them. That situation resulted in the big problem which ensued here.

Hughes: Now, were the local biosafety committees established almost immediately?

¹ The office of the chairman of Biochemistry is located on the ninth floor of the Medical Sciences Building.

² NIH Director Donald Fredrickson issued guidelines for NIH-supported rDNA research in June 1976. On July 7, 1976, the guidelines were published in the Federal Register.

- Rutter: No. But we had always had a safety committee on the campus.¹ There was a clinical safety committee on campus. The committee dealt with the use of animals, with the use of proper protocols in dealing with patients, and with general safety matters and so on. The early versions of the recombinant guidelines required considerable judgment by the local biosafety committee.
- Hughes: So that same committee took on this new responsibility?
- Rutter: A special committee was formed which didn't deal with the clinical guidelines but eventually dealt specifically with the recombinant guidelines.

The Rat Insulin Gene Project

Strategy and Goals

- Rutter: Even before Gordon's death, we were intensely involved in the insulin gene project. We had considered it as soon as the Boyer-Cohen experiments were known. Our strategy was to use our ability to purify the islet cells to obtain a source rich in insulin mRNA. For years, scientists had studied the properties of islets, especially those from fish which could be isolated with a high degree of purity. After several unsuccessful attempts to obtain a good source of fish islets (Brockman bodies) that were found in the gut mesenteries, we decided to use the pancreas of rats which also could be isolated in relatively pure form. At the same time, we were interested in cloning the somatostatin gene and potentially the glucagon gene, all the significant hormone genes of the endocrine pancreas, as well as some of the genes of the exocrine pancreas, so it was a broad program.

¹On March 25, 1975, Brian McCarthy in the Department of Biochemistry wrote to the dean of the UCSF School of Medicine suggesting formation of a "Biohazards Committee". On October 5, 1976, UCSF announced formation of "[a] new biosafety committee...to inventory, monitor and maintain safeguards for research in genetic engineering..." (Brian J. McCarthy to Dean Julius Krevans, March 2, 1975. School of Medicine, Dean's Records, 1936-1987, AR90-56, carton 1, folder 18; News Services Records, 1976-86, AR86-7, carton 2, folder 76, Archives and Special Collections, UCSF Library.

Dr. Rutter's Background in Developmental Mechanisms

Rutter: I had been working on the development of the pancreas for more than a decade. As I told you, I had come from a chemical background and wanted to work on mammalian development. I took a sabbatical at Stanford working in the laboratory with Clifford Grobstein, who was an eminent embryologist. I chose to work on pancreatic development because of the ease of measurement of the differentiative process both morphological and biochemical via the detection of insulin and other exocrine pancreatic enzymes. Clifford Grobstein became the head of the department and later head of Biology at UC San Diego. In that environment I learned experimental embryology, how to culture pancreases and to get them to develop in vitro. I studied the interaction between two tissue types (mesenchyme and epithelium) that are required for normal development, I demonstrated that an extract from mesenchymal cells could substitute for the mesenchymal cells, to signal the pancreatic epithelia to undergo differentiation. That was pretty hot stuff in development at the time. That started a line of research which aimed at learning something about the molecular control of the exocrine and endocrine cells, particularly the insulin, glucagon and somatostatin genes. The studies at Stanford were carried out in 1963.

So when I came to San Francisco, I was working partly on development of these genes and partly on mechanisms of gene expression. In the 1974-75 time frame, I was focusing primarily on the pancreatic genes. At that time, I had attenuated the work on the RNA polymerases, because some of my other students, particularly Bob Roeder, were out there doing a very good job in that field. We focused on the problem of the insulin gene.

My colleague in all of this was Raymond Pictet. Raymond had come from the lab of Albert Renold, a famous diabetologist in Geneva, Switzerland. Pictet was from a famous Swiss family (banking and the law). Renold had spent a sabbatical in my lab at Seattle learning some of the modern approaches to development just before I came to San Francisco. It was Renold who suggested that Raymond stay on with me. At that time Raymond was essentially a morphologically oriented cell biologist and an electron microscopist. So we wanted to couple morphology/cell biology and biochemistry/molecular biology to study developmental mechanisms. It was a good team.

In the early seventies, we carried out a morphological/biochemical study of the developing pancreas which was the first study of that sort and became the definitive study of pancreatic

development. Raymond was very good with his hands and with cell systems and experimentation.

Strategies for Obtaining Islet Cells

Rutter: I was very keen to work on a molecular biological problem and the isolation of the insulin gene was first on this list. We spent a lot of time looking for a preferred source of islets. Fish with a large number of Brockmann bodies contain the islet cells. In the human all of the islets are embedded in the exocrine pancreas which is loaded with RNase and DNase, which rapidly degrade RNA and DNA, respectively. The approach of producing a cDNA from an mRNA library becomes impossible in the presence of significant concentrations of RNase. So we had to develop a strategy that minimized the presence of exocrine pancreas and also inhibited any RNase activity.

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Rutter: One of the possibilities was to isolate Brockman bodies which are essentially endocrine organs (a little like large islets). At first we tried the group at the San Francisco Academy of Science--the aquarium where they have an excellent group working on fish.

Hughes: That was fortuitous.

Rutter: It's really quite an amazing place. The researchers are quite well known and very cooperative. Raymond and I spent a fair amount of time trying to find a local source of fish with well-developed Brockman bodies. The anglerfish is a well-known source, however it exists in the Atlantic. Only a few fish available from the Pacific had Brockman bodies and they were too small to be useful. Furthermore, we discovered that Brockman bodies, although they are largely comprised of endocrine cells also contain a little ring of exocrine cells on the outside. So they're never free of the digestive enzymes.

There were two other strategies. One was to concentrate on islet tumors, which could be grown independent of the pancreas and therefore one could eliminate exocrine cells. This became a hot prospect. A group in Boston, Bill Chick and Arthur Like developed what appeared to be the best tumor cell that could produce insulin. There were other tumor cells that seemed less satisfactory. So I talked with Chick and made a prospective agreement to use their cells for this purpose. Since they didn't

intend to clone the insulin gene themselves, they couldn't easily say no.

Competition

Rutter: A seminal meeting at Eli Lilly [May 1976] was set up to talk about the insulin gene. Both Raymond Pictet and I attended and gave talks. To my surprise, I found Howard Goodman there. I hadn't known at all that he was interested in this problem. Howard had been mostly involved with John Baxter in the cloning of the growth hormone gene. Howard gave a talk on cloning technology. I believed he was interested in cloning an important gene; I was interested in the control of the expression of the insulin gene in embryological development and in the diabetic. Thus we had complementary interests.

At that meeting, two significant things happened. First, when we talked with Chick and Like it became clear all of sudden that our deal was not as secure as I thought it was.

Hughes: Why were they backing off?

Rutter: Because Wally Gilbert also from Harvard had become seriously interested in cloning the insulin gene.

Hughes: You didn't know that he was interested?

Rutter: Previously, I didn't have any idea he was interested in this problem.

Hughes: Why are these people going after the insulin gene?

Rutter: I'm sure that Howard was aware of the possible commercial value of the project. He might have more accurately assessed it than I did or perhaps Axel Ullrich, the key person in his lab who had come from Germany to do this project, wanted a more "important" gene than hemoglobin. So the hormones really became the key targets. Of course, insulin had the advantage of being a small gene and therefore it was to some extent now technologically accessible.

Wally Gilbert was an outstanding scientist, a molecular geneticist who had done marvelous work in developing the sequencing technique. Much of the relevant work in his lab, starting in the early seventies had also paralleled ours. He had become interested in ribosomal and tRNA genes, and we had overlapped and competed in those areas. He was a person of real

talent and resources. When he started a project, he was a major competitor.

Hughes: What did you feel when you learned that the field was far more crowded than you had suspected?

Rutter: It dialed up my competitive spirit. [laughter] I thought it was really good.

Hughes: You like that then. You like working with pressure.

Rutter: I like working both ways, really. I think it's fun to do science alone but it's also fun to do it in competition with others. They both have advantages. In this case, I was in the field already, therefore I was not considering withdrawing from competition. The problem for me personally was that I had departmental responsibilities in addition to my lab interests.

Hughes: Did Wally Gilbert have those responsibilities?

Rutter: No. So it was a complex situation. I considered my departmental duties to be very a significant personal obligation. It was a complex life for me, for sure. As department chairman, I also had to deal delicately with the issues of competition within the department, especially when I was involved.

Hughes: Did you feel that you were in competition with Howard Goodman?

Rutter: Yes, for sure. If he was going to do the same thing as I was going to do, then we would be really in competition. I learned that Howard had already talked with Jerry Grodsky who was in the [UCSF] Metabolic Research Unit. Jerry Grodsky also had worked on the preparation of islet cells that could be used as a source for the gene. But Jerry had no experience in biochemistry and genetics. Hence bringing in Jerry would have made a tenuous three-way partnership.

So I talked it over with Howard. Pictet had had much more experience than Jerry in purifying islet cells. Furthermore, we had done a lot of work on the isolation of those fish islet cells and on the development of a process for destroying the RNase. That was the other alternative: to get rid of the destructive enzymes in the pancreas.

Hughes: Were other people working on that avenue?

Rutter: There were quite a few people who had considered it but nobody productively. We thought we had the biology and the chemistry parts in control more than anybody else, and we'd worked with the

pancreas. We had cloning experience, though not of cDNAs; we had done a lot of cloning of ribosomal RNAs and the whole transcription system of yeast. We were technologically up-to-date.

The Players at UCSF

Rutter: But Howard and his group had the most sophistication in cloning per se. He developed those technologies. So we decided in the end that we would collaborate. Axel Ullrich was the key person to work on the insulin project. Howard's lab was run more on the basis of individual choice than on the basis of a directed approach. That fit with Howard's focus on technology per se, with a secondary interest in application to x, y, or z problem. So it was quite appropriate. Peter Seeburg wanted to work with growth hormone, and Howard began collaborating with John Baxter on this problem. Baxter had also trained for some period of time with Gordon. But Gordon and John had become estranged because John was so aggressive and wanted essentially to work on the same things that Gordon did. Gordon at first very strongly supported John as a member of the faculty but then withdrew his support. I was more or less left holding the bag.

Hughes: But John remained in Tomkins' lab?

Rutter: No. On Gordon's recommendation John had accepted a faculty position in the Metabolic Research Unit. From Gordon's lab, besides John Baxter, we had David Gelfand who was interested in gene expression, Keith Yamamoto who was interested in expression but against commercial interests in the department, and Patrick O'Farrell who was also very ingenious methodologically and contributed broadly. When Gordon died, I had to manage his lab. To some of the very best postdocs like Keith Yamamoto and Pat O'Farrell, we offered faculty positions to stabilize their position here. Gordon also had others working on a variety of subjects, so I had to oversee these folks and at the same time try to go like hell on the insulin project.

Hughes: Could you really do all this?

Rutter: Well, it kept the mind alive to the limit. [laughter]

Hughes: Understatement of the century.

Rutter: So anyway, we were very busy. Howard was a difficult person to collaborate with. In every collaboration, he sensed himself as

being more or less a little disadvantaged. So he was angry with Herb because he thought he should have been on the Cohen-Boyer paper (though according to Cohen, he had not contributed to the ideas, nor the execution of the experiments).¹

Hughes: Was there any justification for Goodman's dissatisfaction?

Rutter: He had been collaborating with Herb on the EcoRI restriction endonuclease problem and other restriction enzymes which had been used in the studies. Howard was technically great, very ambitious but not necessarily biologically farsighted. Because of that, he was really well suited for collaborations. Everybody else appreciated him as a collaborator but he was unhappy as a collaborator. Of course, that was the situation which occurred with us. He always wanted to segregate experimental roles and credit. So he negotiated constantly, attempting to keep us in a restricted role, and particularly not involving us in cloning.

Hughes: Yet each group needed the other.

Rutter: Each group absolutely needed the other in order to make the project competitive. Howard's idea was for us to provide the RNA and Axel would do the cloning per se. From our side we wanted to do cloning experiments also. We were using this [technique] in other fields and felt that it wasn't disadvantageous to have parallel cloning efforts.

Jerry Grodsky also wanted to get into the game. Although he was technically a member of the department, he was housed in the Metabolic Research Unit. He wasn't part of the core departmental group and in all fairness to us, he hadn't participated truly in the development of the department and he did not contribute technologically or biologically. If he had been working in this field or had shown a strong intent to use modern methodologies, there would have been every reason for him to be included. But as it was, his only contribution was to essentially prepare islet cells. He was more pain than he was worth. Raymond Pictet had more experience in this area. Also, we had tried previously to collaborate with him and he didn't contribute much. He knew a lot about diabetes but when it came to these new approaches, he was not of much value. So we eliminated him from the project.

Hughes: How did you do that?

Rutter: Just by telling him that he was not on this project.

¹ For more on this topic, see Cohen's oral history in progress.

Hughes: Hadn't Ullrich been the one particularly working with him?

Rutter: Probably, unbeknownst to Howard, Ullrich had already talked to Jerry Grodsky about the project. They never started to work with Grodsky but he had contacted him and Grodsky may have felt he was a collaborator. However, the agreement between Howard and me bypassed Ullrich and Grodsky. In this respect, Howard began executing some authority over Axel. Axel was entrepreneurial; he was a determined individual who bridled at any kind of control. Howard was almost legalistic in his approach; he would write things and worry very much about the word crafting and so on, but perhaps not obtain an understanding with his colleagues. As I mentioned, he had many good qualities, but his personal relationships were not strong. So his relationships with his lab colleagues were authoritarian and somewhat distant rather than friendly. Despite that, there were a lot of good social interactions.

More on the Problem of Obtaining Islet Cells

Rutter: During the course of the work, we had many different approaches to obtaining islet cells. We were eliminated from [screening] Chick and Like's cultured islet cells. John Baxter tried to get some islet cell tumor from somebody else and deal himself into the program.

Hughes: Somebody from another institution?

Rutter: Yes. He got some tumors from a group at NIH. As it turned out, he was trying to obtain somebody else's islet tumors, which was a little bit out of the way. John was fairly well known in the clinical community. Many of the clinical people at that time didn't know the value of the tissues they had in their refrigerator. John attempted to get the cells/tumors and thereby become a principal in the project.

We worked intensively on the problem of destruction of the RNase. At the outset, it was very difficult because RNase is very stable. One could boil it and it would refold. It's one of the most stable enzymes known to man. John Chirgwin in my lab, along with two or three other people, Raymond Pictet, Pablo Valenzuela and I, began focusing on this issue because we didn't have any other alternative. The issue, obviously, was to get enough material. So we knew that Gilbert had what looked at that time to be the best source.

Hughes: The insulinoma.

Rutter: The Like-Chick insulinoma.

However, there was another alternative biological system. In early embryos, the proportion of islet cells to exocrine cells is high. In a newborn calf, for example, 30 percent of the cells are endocrine cells, whereas in an adult, it's 1 percent. So if one could obtain embryonic pancreases from any animal, this could be a good source.

So we began to look for a source. There were no abattoirs in California. In the last several years, they had been all phased out. We found that Grady Saunders' lab at the University of Texas was employing calf pancreas. In Texas they still had stockyards and abattoirs. So I sent John Chirgwin down to Texas to obtain some calf pancreases. At that time, one of Grady Saunders' students, Peter Lomedico, had decided to come to my lab as a postdoc. Chirgwin worked with Lomedico attempting to isolate cDNA enriched with insulin cDNA from this source. With his method, which at that time was not perfected but still better than other methods, one would destroy most of the RNase and thereby get enough mRNA so that you could make cDNA to get the message.

Hughes: And the little bit of exocrine tissue?

Rutter: It was a danger but we thought it was much the best source because the prep was so tremendously enriched to start with. That method turned out to be impractical. We couldn't get enough tissue; the lab wasn't set up properly; there was another research project going on there.

Meanwhile, Wally Gilbert recruited Lomedico away from us. Wally persuaded him that his lab was the best place to do insulin cloning. That was more evidence that the competition was really intense. Furthermore, if Peter had come to my lab, we would undoubtedly have tried more intensively to work on the calf system.

Hughes: Which route did Wally Gilbert take? He was using the insulinoma?

Rutter: He used the insulinoma but with Lomedico there he could have chosen the calf pancreas as well.

Hughes: You weren't going to use the insulinoma because you couldn't get it.

Rutter: That's right; Wally blocked that.

Hughes: Was that a not-too-subtle way of trying to do you in?

Rutter: Oh yes, of course.

Hughes: If Gilbert was going the insulinoma route, why did he need Comedico?

Rutter: It was just another aspect of the intense competition that had sprung up. So it became obvious that we didn't have the luxury of taking the time to develop the calf pancreas approach. We had to use the methods we had. So we pushed John Chirgwin extremely hard on the RNase problem.

A Method for Controlling RNase Activity

Rutter: Using two different strategies of denaturation, simultaneously we were able to virtually totally control RNase activity. This was a very significant achievement. That method is still one of the most quoted methods; it provides everybody an access to mRNA.

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Hughes: Did you make that methodology available?

Rutter: We published it.¹

Hughes: Was there anything that you were keeping to yourselves at that juncture?

Rutter: Not really, except for its use in isolation of insulin mRNA.

Hughes: Was that true of every group?

Rutter: I wouldn't say so. But my philosophy, at least up until that time, was always to report results, but also to patent useful information. If you couldn't run faster than the competition, why we deserved to lose.

For rat cells we needed this method, and it worked. We could get cDNAs. At the same time, Howard's whole lab was devoted to the cloning of the gene. He had John Shine, an Australian, who

¹ J. M. Chirgwin, A. E. Przybyla, R. J. MacDonald, and W. J. Rutter. Isolation of biologically active RNA from sources enriched in ribonuclease. Biochemistry 1979, 19:5294-5299.

was exceptionally able. John worked on increasing the efficiency of the cloning procedure. He made some extremely important contributions, along with Axel Ullrich and a technician, Ed Tischer with Raymond Pictet and John Chirgwin.

Hughes: Are those the players in the cloning of the rat gene for insulin?

Rutter: Yes, those were the original players. Later, Graeme Bell. Graeme had done his doctoral research with me. He was technically very adept. We wanted Graeme to focus on cloning the human insulin mRNA.

About the time that all of this was happening, Genentech was going strong.¹ At first there were no formal rules for recombinant DNA research, and we were cloning on bench tops. Then the RAC was established and there was an intense interest in the details of cloning, including the vectors and the cell lines employed. New vectors were being developed that were crippled so that one could not get expression in the wild.

Hughes: I know that Boyer was one of the main contributors.

Rutter: Boyer was a main contributor to the development of effective expression vectors. His lab was sharply focused on vectorology. There were vectors developed by Mary Betlach (pMB9). Then there was pBR322 (Betlach/Rodriguez). Therefore, once we prepared good cDNA we felt we could clone the cDNA. An enriched source of insulin cDNA was crucial, and the islet cell has one function, to produce insulin. It produces it much like the red cell produces hemoglobin. The high level of insulin mRNA in these cells makes it easier to obtain the insulin cDNA among the cloned cDNA.

The Ingredients of Success

Rutter: Once we had gotten a good way of purifying the cells and had obtained enough of them derived from several hundred animals in preparation at a time, and the RNase procedure worked, then the production of the cDNA and the cloning of insulin cDNA became a question of probability, because we had no other way of identifying which clone was which.

¹ Herbert Boyer and Robert Swanson incorporated Genentech on April 7, 1976.

Because the purification of the mRNA was so good and the cDNAs were intact, it turned out that we had a lot of cDNA and it was highly enriched. As it turned out, the tumor cell source which Wally was using didn't produce much insulin so it wasn't as highly enriched in insulin cDNA.

Hughes: But you didn't know that at the time, did you?

Rutter: No. But it would have come out in the experiments. We might nevertheless have chosen rat pancreas islets since we knew that they had such high concentrations of insulin cDNA.

Hughes: How did you know that?

Rutter: Bill Chick and Arthur Like described their cells as high producers of insulin. They had secretory granules. However, we had characterized the beta cells in development, so we had experience that others didn't. It would have been obvious as soon as we began to work with the cells that the islets had more secretory granules. Thus we had rat or mouse islets available.

Furthermore, we had good vectors as a result of the work of Herb's lab. pMB9 had a low cloning efficiency because the selection procedure was inefficient. This issue was solved in pBR322 by counter selections. It was an excellent vector.

Hughes: Did you have a jump on that vector?

Rutter: Yes, for sure, in the sense that it was available in the department. On the other hand, it was also available to others. Herb shared the vector.

Hughes: So the Genentech issue didn't interfere with the availability of these vectors?

Rutter: No, that vector didn't belong to Genentech. That work and other projects in Herb's lab were supported by NIH funding.

Hughes: Were there instances in which it was difficult to tell what was Genentech's property and what was the university's?

Rutter: To some extent, because Genentech started working on specific expression projects. As I told you, there were concurrent studies on expression of heterologous genes that were carried out at UCSF. A patent for expression was subsequently awarded to Genentech. In my view, it should not have been awarded to Genentech. It should have been awarded to four young scientists at UCSF. I felt that Genentech was overly aggressive in obtaining early rights to intellectual property. On the other hand, as far as research was

concerned, those methodologies were available to us. Most of the work was supported by NIH.

Genentech's Approach to the Insulin Gene

Rutter: Genentech was primarily working on insulin. We knew at that time that Keiichi Itakura and colleagues were synthesizing the sequences coding for the two chains of insulin. Insulin is synthesized via a single chain precursor and the connecting peptide is subsequently chopped out. Then the mature insulin is comprised of two chains, which on the precursor are connected by a peptide, so a two-chain molecule is made from a single chain called proinsulin. For Genentech to synthesize the proinsulin molecule was a difficult job indeed. Synthesizing the two single chains, however, was much, much less difficult. Then they would combine the chains.

Others had shown that one could combine the chains chemically. A professor in the Department of Biochemistry at Berkeley, Fred Carpenter, had studied this process thoroughly. In fact one of the people who worked on this is now director of research for Bayer (Wolfgang Busse).

The Genentech group clearly realized that they could synthesize the chains by using Itakura's synthetic talents. They could express the chains; they could combine them using Carpenter's technology to make insulin. That was their approach.

The NIH Guidelines

Hughes: Do the NIH guidelines enter in here? You were working from an academic base and Genentech, of course, was a commercial base; the NIH guidelines were voluntary as far as industry was concerned.

Rutter: That's right. Therefore industry had, to some extent, less of a requirement to follow them. The universities agreed to fully subscribe to the guidelines, so we were conforming and Genentech didn't necessarily have to conform. I can't speak for Genentech because I don't know exactly how they treated the guidelines. However, I believe companies had to be careful of the guidelines.

Hughes: Why?

Rutter: The FDA [Food and Drug Administration] might not approve a product that didn't adhere to the guidelines; there was a lot of indirect pressure to adhere, but there was no direct pressure to my knowledge.

Hughes: Did Genentech use a P3 lab?

Rutter: All industrial labs eventually used P3 labs. Everybody conformed to the guidelines. They might have chosen not to do the initial cloning experiments in P3 facilities. I just don't know.

Hughes: I thought because Genentech was taking the chemical route to synthesize insulin, the requirement for a P3 facility didn't apply.

Rutter: That's absolutely true for a non-cloning strategy. That was one of the reasons why they chose that route. All the rest of the competitors had to obey the guidelines. Genentech just bypassed all that. Each of the chains, of course, is not dangerous because it is not active until you put the two together. So collectively that made a good deal of sense for Genentech. It was hypothesized that if one has E. coli that could produce insulin, then theoretically insulin could be absorbed by the gut, and we would all die from hypoglycemia. This became a really serious issue with us. There had been experiments in which insulin was introduced in the gut. The absorption was so inefficient it would have been impossible to become hypoglycemic because there is such tremendously active digestion of insulin. This was a time of great fear regarding recombinant DNA research, and unlikely or impossible scenarios were considered quite plausible.

Let's stop here.

The Rat Insulin Gene Project (cont'd.)

[Interview 6: May 25 and May 31, 1992]¹ ##

Studies of Pancreatic Differentiation

[Session 6 and Session 10 address the cloning of the rat insulin gene by the Rutter-Goodman laboratory groups. Session 6 was recorded before Dr. Rutter had been deposed for the UCSF, Eli Lilly, Genentech insulin gene patent case. After his deposition, Dr. Rutter asked to have a second discussion. The result is Session 10. Dr. Rutter edited both sessions heavily over the summer and early fall of 1997, making stylistic changes, omitting largely redundant material, clarifying, and occasionally adding new information, such as his reference in Session 10 to the certified letters that he and Goodman exchanged in the spring of 1977. The inevitable repetitions occurring in two discussions of the same subject have, for purposes of comparison and amplification, been allowed to stand.]

Rutter: My laboratory consisted of twenty to thirty individuals whose interests were focused in three different areas. One of them, which I described earlier, was the pancreas, that I had begun to study in the early 1960s as a way to understand specific gene expression in particular cell types. That interest had started on a year's sabbatical at Stanford with Clifford Grobstein. It developed to the point where we studied the interaction between two types of cells (epithelial and mesenchymal cells). This interaction was necessary to get the differentiation of the pancreatic epithelia. Whereas a number of experiments had been carried out at the gross biological level, we began to simplify the system by getting extracts from mesenchymal cells to support differentiation of the epithelial primordia.

Those observations were quite unique in that field. They suggested a strategy for identifying the specific molecules that were important in the differentiation process. They also started an avenue of research which led to the genes that were turned on as a result of the differentiation process in the exocrine pancreatic cells and also the genes that were turned on in the endocrine pancreas (including insulin and glucagon). This work attracted a fair amount of attention in the field of embryonic development.

¹ The discussion recorded on May 31, 1992 replaces a fifteen-minute segment recorded on May 25, 1992, which was inadvertently erased.

One of the key diabetic endocrinologists from Geneva, Albert Renold, came on a sabbatical to visit my lab in Seattle, Washington, just before I came to San Francisco. He brought with him a young Swiss named Raymond Pictet who was an electron microscopist by training, also a good cell biologist but had also studied diabetes. He was an M.D. but trained in the academic tradition and was an excellent technical person. So Renold came over to become more intellectually familiar with the science. Raymond actually performed experiments and stayed on with me then for more than fifteen years and was a major contributor and colleague.

In the early seventies, he and I began a morphological description of the development of the pancreas that was coupled with the biochemical description of the proteins that accumulated during differentiation and the patterns of gene expression. These were basically the fundamental studies in this field and formed the basis of our interest in the genes that were specifically associated with the exocrine and endocrine pancreas. Clearly, insulin was the particular gene of most interest.

In the middle sixties, I became interested in the process of gene expression per se. I started a program that was directed to defining the enzyme systems which transcribe DNA. Bob Roeder, a graduate student, and I discovered three enzymes which essentially were the fundamental components of the systems that read out the genes. One enzyme transcribes the genes which make proteins, another transcribes the genes that make ribosomal RNA, and another transcribes the genes that make small RNAs. Clearly, this specificity was the basic element of the system which allowed specific transcription of one particular gene or another. This was especially true for the enzymes that transcribe the genes that encode specific proteins--the messenger RNA transcribing enzymes. This was a very significant program so I had a number of people working on characterizing the enzymes themselves with the intent of elucidating the mechanisms of specificity.

In the middle seventies I had a good group of people working on the enzymes themselves and another group of people working on the genes that were transcribed by these enzymes (ribosomal genes for polymerase I) and also the tRNA [transfer RNA] genes (polymerase III).

Key Laboratory Personnel

Rutter: The key figures in those two programs at that time were Pablo Valenzuela who, together with Graeme Bell and several other individuals, worked on the genes. They were attempting to clone them and describe their characteristics and their mechanism of expression. The pancreatic endocrine group was of course focused on the specific genes that were transcribed somehow by polymerase II. Raymond Pictet by the middle seventies had become quite a sophisticated molecular biologist. He wanted to clone the insulin gene and was a key figure in developing the biological system from which the cDNA could be obtained. Raymond Pictet focused on the pancreatic islets that he knew very well.

The development of a method for preparation of the mRNA was carried out by a very smart but also unusual person named John Chirgwin. There were several others in the laboratory that worked on this project as well--Raymond MacDonald, who is now at the University of Texas, and Jeffrey Edman, now a faculty member at UCSF. I won't mention all the twenty or so odd people that played a role in various aspects of that program.

John Chirgwin obtained his undergraduate degree from Harvard, and he got his Ph.D. from UC Irvine where he worked on a protein chemistry project. In the insulin program, he had to develop a method which would allow isolation of intact mRNA species from a tissue which contained large amounts of RNase, an enzyme which hydrolyzed RNA. The enzyme was also notoriously stable.

I'll focus on the people in Howard Goodman's lab who became involved in this project. In the late seventies, Peter Seeburg and Axel Ullrich came from the University of Heidelberg in Germany. Both came from the same department. In fact, I think both of them had worked for Heinz Schaller at Heidelberg. They came wanting to work very aggressively on a cloning project on an important gene.

Another key figure was John Shine, who hailed from Australia. John had already done some beautiful experiments elaborating the sequences signalling the initiation of transcription in bacteria. These are still known as the Shine-Dalgarno sequences. John was a very thoughtful, ingenious, and technically adept person who worked on cloning methodology. Essentially he developed methods to enhance the probability that clones that were isolated in bacteria contained the desired insert. Clearly, the value of a vector or plasmid which grew inside bacterial cells for cloning was related to its ability to

accept a cDNA (which was produced by reverse transcription of a messenger RNA). In some way, one needed to get the ends incorporated with high yields into the plasmid or the vector.

There were a variety of methods that were used to accomplish this: the production of "sticky ends" produced by tailing with specific complementary nucleotides that would hybridize one with the other, or by using restriction enzymes which produced a long enough overlap so that there would be a precise orientation by hybridization of the molecules. John realized that such combinations could depend upon the degree of phosphorylation of the ends; he developed a method to essentially enhance the combination in the ends. The net result of his studies was that it greatly facilitated one's ability to get high efficiency incorporation of messenger RNA.

Seeburg then focused on the cloning of the growth hormone cDNA. Perhaps this interest was influenced by John Baxter, who had been a postdoctoral associate and protégé of Gordon Tomkins and a professor of endocrinology in the Department of Medicine. John was a bright, very aggressive, and forward-thinking individual. He had developed a laboratory that wasn't widely respected for its technical competence but he clearly saw the power of molecular biology and wanted to enter this field. In order to do so, he interacted mostly with Howard's lab. He made friends with Peter Seeburg and also John Shine, and established a cooperative program that blended his own knowledge of biology and medicine with Howard's technical competence.

Axel Ullrich was an affable individual who was very ambitious and sophisticated, driven to success. In my experience, he and Seeburg were the first to be concerned about accreditation and attribution. Previously, people were more trusting and less concerned with who got credit, at least before the experiments were done. They were more agreeable to cooperative studies. These individuals [Ullrich and Seeburg] really foresaw the importance of these studies, and the notoriety that would come from carrying out experiments like this. They essentially prenegotiated their roles in the experiments that were to be performed and therefore prenegotiated essentially their positions in the authorship on papers.

Individual and Laboratory Styles

Rutter: Howard Goodman I think was quite happy that the people in the laboratory took separate projects, and he himself liked to be

independently working on a different project. So he wasn't the kind of person that would bring a group together to solve a complex problem. Rather, he gave individuals the right to do what they could.

Hughes: As department chairman, could you have done something about the prenegotiation, fostering a more cooperative outlook?

Rutter: In fact, I tried. Indeed, I fostered cooperation between labs and individuals, because the projects could progress more rapidly (and competitively).

Hughes: Ullrich's and Seeburg's wasn't a European approach as far as you knew?

Rutter: It could have been a European approach. Many of the Germans were in big labs. They were given very specific things to do and their future depended upon the success of their phase of the project. Frequently individuals worked in coordinated groups. In these instances, of course, ambitious people like Seeburg and Ullrich wanted very much to do the most important phases of the experiments. Howard, of course, supported this approach because it emphasized his role as well. So this style led to a less than open relationship. The data was shared, but not in real time.

Progressively over a period of time, as I mentioned last time, relationships between our groups became more and more fractious. As the project proceeded, a potential conflict developed because Axel wanted to do all the crucial experiments. Of course, that wasn't to be. Similarly, Peter wanted to do all the important experiments with growth hormone.

John Shine was a more agreeable collaborator. He worked on both projects and was, I think, more cooperative and generally easier to deal with. I didn't mean to imply that Axel was difficult to deal with. As I said before, he is a very bright, charming person and well-liked at the personal level. He was fun at parties and so was Peter. At the personal level, we really had a very good time. It's just when it got down to getting things done in the laboratory that we had problems.

Hughes: Was there static?

Rutter: Static? What do you mean by that?

Hughes: I mean, was there overt friction?

Rutter: To some extent. We had lots of conversations among Axel and Howard and myself. There wasn't really static between the

laboratories but between competitive labs. Later on, after the rat insulin gene was discovered, and Graeme Bell from my lab came into the project to work on human insulin cloning, there was some real friction with Barbara Cordell (from Howard Goodman's lab) because we were working on parallel paths. We didn't have people shouting at each other, but there was a real competition. People were cordial but they didn't always tell everybody what they were doing, share reagents, or help to solve problems together.

Hughes: Which was unlike the prior situation in the department?

Rutter: For sure. Our department was a very open place in the seventies, a remarkably open place. Even during this period, there was a lot of technological exchange, good personal relationships, and cooperative projects. But there was a special intensity about the insulin project. Everybody wanted to win, first against external competitors and then second against internal competitors, (hopefully in that order).

Vectorology

Hughes: Let's fit Boyer and his vectorology into the picture.

Rutter: Yes. Boyer began developing vectors that employed some of the restriction enzymes he had been studying but also phage systems that could be used for gene transfer into bacterial cells. His program was immensely important to the field (and to us) because at that time the efficiency of transfer was critically important. The messenger RNA was limited. The efficiency of cloning the plasmids containing inserts was very important because characterizing them was tedious and effectively determined the feasibility and rate of the cloning process.

Herb and Mary Betlach had developed a vector which was the initial approach to double-selection systems, which increased the efficiency of cloning. A transformed cell either doesn't contain the plasmid (in which case it doesn't display the characteristics of either selection system) or it contains a plasmid and elicits the characteristics of one. The most advanced selective systems are ones in which you have a single positive selection mechanism coupled to a negative one (in which the insert disrupts a marker).

The first vector of that group was pMB9, developed by Mary Betlach. One of its selections was based on colicin which was difficult to screen. So pMB9 was very difficult to use as a vector as compared to pBR322, which was developed by Paco Bolivar,

a talented Mexican scientist, and Ray Rodriguez. Paco is now back in Mexico, a distinguished molecular biologist there, and Ray is on the faculty at UC Davis.

Hughes: What was the time interval between the development of the two plasmids?

Rutter: I can't tell you precisely, but it was about a year as I remember it.

Hughes: And it was immediately apparent that pBR322 was much superior?

Rutter: It was superior, not only from the standpoint of selectivity, which was important for laboratory work, but also other things in the vector had been changed such that there was a much lower level of transfer of this vector into bacteria, other than the severely limited strain used for cloning. Thus it was safer.

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Rutter: It was safer because of the ability to destroy the cell by either a penicillin-like antibiotic or a tetracycline-like antibiotic or both. That wasn't the case in pMB9 because it produced colicin, a much more difficult antibiotic to use in selection.

On the other hand, the vectors were by and large similar in structure. There weren't novel components in the vectors; they were part of the same family essentially, but in the case of pBR322, different parts of the vector were removed and a single antibiotic resistance gene inserted.

That being the case, nobody could understand why pBR322 wouldn't be approved by NIH immediately after, or at the same time as pMB9. If there were a safety issue (and nobody believed there was), pBR322 was obviously safer than pMB9 because of one's ability to control the antibiotics. Secondly, the other parts of the virus had been removed, so it was a smaller vector and that obviously meant less chance for any other genes via recombination to produce a vector which could be viable in another organism. That being the case, the delay in [NIH] approval didn't make intellectual sense.

Herb's development of these vectors was a key contribution, not only to our work but to other work going on in the United States. The small group of people within his lab who continued to develop better and better vectors really made an excellent contribution to science. Subsequently, other groups developed even better vectors, but these were the best at the time.

Clearly, Herb's program on vectors then complemented the other programs on cloning technology at UCSF. These were centered in Howard Goodman's lab, with Howard himself working on sequencing and data collection. Other key contributors were Peter Seeburg and, to some extent, Axel. My lab worked on preparation of the mRNA.

The P3 Laboratory

Hughes: The other element we need in this history is the P3 [physical containment level 3] lab.

Rutter: Yes. After the institution of the [NIH] guidelines, it became important to construct a facility which operated under secured conditions--basically conditions similar to those that would have been employed if you worked with dangerous microorganisms. We didn't have any facilities at UCSF which could meet the fastidious standards of the NIH guidelines. Of course, other labs were working on demonstrably dangerous organisms, but these were not so tightly regulated as those working with recombinant DNA.

There were two old labs on the tenth floor of Health Sciences West that we could renovate. One of the virtues of UCSF at that time was that they allowed me considerable budgetary freedom. So we managed to get the funds required to renovate these labs in a very short time and place in them the equipment that was dedicated to the cloning process.

One entered into an anteroom and then into the P3 facility itself. We set up a signout book¹ very much like the signout book that we used on any one of the major pieces of equipment or facilities. Researchers could use the P3 facility once they had been cleared to do so. We set up a small faculty group to oversee the process and the facility. At various times, this included Herb Boyer, Howard Goodman, and Brian McCarthy, who was a molecular geneticist but who was levelheaded and was himself not involved in any one of these experiments. Brian and this group established the appropriate procedures.

Hughes: Your choice of McCarthy was specifically because of his noninvolvement?

Rutter: We tried to choose people who knew the processes involved in cloning and hence would oversee the facility in a sophisticated way, always keeping "safety" and the guidelines in mind. Brian had worked with microorganisms, did know the field very well, and

¹The signout or logbook was "formally instituted" on December 27, 1977, after the P3 facility was already in operation. (Regulations concerning use of P3 facility, n.d., News Service Records, 1976-86, Archives and Special Collections, UCSF Library, AR86-7, carton 2: folder 76. Hereafter, News Services Records.)

ultimately became a major player in it. But he was not involved specifically in these experiments. Therefore, we felt that he was an objective individual who was also not aligned with any of the labs. We were also aware that there could be competition between the various individuals in the department. It was important to have an individual who was objective, had the respect of the scientists, and had a straightforward managing style. The facility operated on more or less an "as-needed" basis. After signing up, people could go in and use the room, understanding what its purpose was.

Hughes: No special training in safety technique was required?

Rutter: Yes. Anybody using the P3 facility got some specific training.

Hughes: From whom?

Rutter: From one of the more experienced scientists who knew the guidelines and was serious about their enforcement. Although few believed that cloning was "dangerous", the facility was run as if it were a dangerous situation.

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Rutter: Understand that none of the scientists had ever worked in a totally clean facility. So there was a learning period during which everything was set up to operate under these restrictive rules. We tried to get in other more sophisticated containment facilities elsewhere to do the cloning, but these were unavailable.

Hughes: It was essentially a department committee.

Rutter: It was a department committee.

Hughes: Why was it set up that way?

Rutter: Well, because it was used by the department. Maybe in hindsight we should have used some external security groups.

Hughes: Critics could argue that it was the fox guarding the henhouse.

Rutter: Not only could, but did, but not at the time. Things were not as legalistic in those times. There were no real laws, but people paid attention to the guidelines, I thought. In principle, if somebody wanted to do an experiment involving clear liquids, in clear tubes, they could be done outside of that facility. They could be done anywhere; you could do them in your kitchen if you had the reagents. In some sense it's a totally artificial

circumstance: guarding the P3 facility doesn't restrict one from doing these experiments elsewhere. Hence, any structure that is set up (short of absolutely having an external group control the necessary reagents) is artificial. It has to be based on trust. Conformance with the guidelines must be recognized to be in one's best interests.

I was convinced that those who were in charge of the P3 facility had a real interest in making it work. They developed a facility with the necessary issues of containment solved, with all the equipment in, there was a good sign-out sheet, etc. Of course, many people observed the use of the P3 facility. I think I would have known quite soon if there was any flagrant misuse of it, because it would have been reported.

Hughes: Yet you were criticized for improper entries in the logbook.¹

Rutter: You're talking about Axel and Peter Seeburg?

Hughes: I don't know; I couldn't tell you that.

Rutter: Well, there were irregularities in the sign up of the logbooks.

Hughes: I am talking about entries which had been made retrospectively, and also apparently there was some discrepancy in reporting a change in vector. This came out in the Wade article.²

Rutter: Yes. That was true; at the beginning there were some irregularities. I believe that was due in retrospect to the voluntary entry system. All entries should have been countersigned by another person who had no involvement in the experiment in question.

Hughes: Presumably these committees had been set up wherever recombinant DNA research was going on. It sounds as though it's almost up to the institution or the department, as the case may be, to decide what the rules are.

Rutter: That's true, even today. It's up to each institution to develop the details of its regulatory program, following of course the general guidelines set up by the NIH. Each institution has a committee which establishes a mechanism to develop and enforce the regulations. If you were to compare this with standards of top

¹ Stephen S. Hall. Invisible Frontiers: The Race to Synthesize a Human Gene. Redmond, WA: Tempus Books, 1987, p. 172; Nicholas Wade. Recombinant DNA: NIH rules broken in insulin gene project. Science, 1977, 197: 1342-1345.

²Nicholas Wade, "Recombinant DNA: NIH Rules Broken in Insulin Gene Project." Science 1977, 197:1342-1345 (September 30, 1977). Hereafter, Wade in Science 1977.

secret national defense laboratories, this would be very amateurish, right? [laughter] That's what, to some extent, was expected by the Senators and their staff at the congressional hearing.¹ Some of these people, for example Senator [Harrison] Schmitt, had been affiliated with national defense institutions, and of course we looked like a bunch of hokies [in terms of our safety regulations] compared to them.

Hughes: Were the local guidelines supposed to conform to whatever RAC [Recombinant DNA Advisory Committee] came up with as the overall guidelines, which, the way you're telling it, had not really been defined yet?

Rutter: Emphatically yes.

Hughes: So you've got a committee trying to regulate a local situation in conformity to a national protocol which doesn't exist?

Rutter: Well said. Certainly at that time a national protocol did not exist. We were talking about issues of security, etcetera, but definition of the degree of security was poorly defined. And of course, as I said before, nobody locally was trained in security procedures.

Typically in every one of the labs there is a sign-up sheet for using expensive or often-used instruments. I'm afraid that the P3 lab operated as an extension of that principle. We had put the P3 facility in a totally different category: the people who were not approved should not go in the P3 facility, the rules were to be strictly abided by, etcetera, etcetera. Clearly, the sign-up sheet that was involved was out there where everybody could see it. It was based on the honor system. It worked nearly all of the time.

Now let me say that with respect to tampering with the logbook, I think that the evidence indicated that there were retroactive changes. On the other hand, these may or may not have been indicative of any wrongdoing. I know from my own personal experience that I have unknowingly made a false entry due to preoccupation with something else.

Hughes: The erasures were brought out in the Senate testimony as indication that the wrong plasmid was being used?

Rutter: The implication was that there was a deliberate cover-up.

¹At the request of Senator Adlai Stevenson III, Drs. Rutter and Boyer testified before the Senate Subcommittee on Science, Technology, and Space on November 8, 1977. For a draft of Rutter's prepared testimony, see Testimony before the Senate Subcommittee on Science, Technology, and Sapce, November 8, 1977. (Rutter correspondence, MSS 94-54, carton 2, folder 24.)

Hughes: I see.

Rutter: In a case like this, the worst interpretation is the one which is favored by the examining group.

Repeating the Gene Cloning

Rutter: However, once we decided to destroy the clones, to the best of my knowledge, Axel did destroy those clones. We talked about how to destroy them by acids or base--DNA (acid), RNA (base).

We believed that since there was a high proportion of clones that were positive for insulin that we could repeat the process in pMB9 using the same material (RNA) that we had used in the pBR322 experiments. We were all intensely interested in repeating the experiments as fast as possible. The two groups worked together very well. There was a real incentive! We did in fact get clones and sequence data very quickly thereafter. It was a pretty effective organization as far as deriving the sequencing information from the clones.

Hughes: Some people thought it was too effective; that it was impossible to do the experiment again in three weeks.¹

Rutter: That's certainly true. However, the cloning process itself is very short. The sequencing had to be performed very rapidly; we were one of the best sequencing groups. John Shine was a whiz at sequencing and was very well organized. The only comment that I made then and I still make is that right up to the end we were changing sequence. Putting the final touches on the paper and putting in the final sequence information occurred virtually at the same time. I remember very much helping to rewrite the paper before we had all the sequence data, getting all the parts of the paper together, while analyzing the sequence data. So it was a very efficient program. This is the first time I'd worked with Howard, but we worked together very well in writing papers, which is also sometimes a big problem. So writing the paper was a relatively simple matter with everybody coalescing.

¹ Wade in Science.

Destruction of the Insulin Clones

Hughes: There was some doubt that the clones actually had been destroyed, or they had been tampered with. Chirgwin apparently came to you and asked not to be included in any publication that came out of the work. He feared that the sequences might be clipped out before the clones were destroyed.¹

Rutter: Yes. John came to me and talked to me about that issue. He didn't ask to be withdrawn from the paper. Clearly, he could have withdrawn at any time; it wasn't a problem with me. Part of this was due to the fact that Axel, in my view stupidly, was adhering to this notion that he had to do everything with those clones. He wouldn't really allow participation from our side. He obviously wanted to be the first on this paper. There was going to be no argument about that.

As the progress culminated in sequence information, the two groups began to fractionate, because after we produced the good RNA and the cloning was working, naturally we wanted to get in[to] the rest of the technology. And Axel absolutely wanted us to stay out of it, despite the fact that we were doing other cloning experiments in the lab. Eventually, this became a real contentious subject.

It's in that context that I think John came in, believing that they could be more cooperative. He thought they must be hiding something. And he was concerned about it. I told him that I was also concerned, had been concerned, and that we had done as much as we could.

But in the end there's no way to tell. There really is no way to tell! Either you do the experiment yourself, so that you know what has happened, or you are uncertain. There's virtually nothing one can do in circumstances like that, unless you carry out the experiments cooperatively. We tried to open up the research group so we would have done it cooperatively (in which case we would have known exactly what was done). This was not practical at that time.

Hughes: Your desire to be cooperative was because you wanted to share in all the aspects of the research, and/or because you wanted to make sure that the clones had been destroyed?

¹ Hall, p.137.

Rutter: It was to participate directly in all aspects of the research. I was not personally concerned that the clones had been destroyed. We had depended on Axel directly, and I had talked to him directly about this. I was personally convinced that he was going to destroy the clones. I was also personally convinced there was a high probability that with our cDNA preparations, they could be recloned. I also was not as concerned with the competition as being able to do the work ourselves, because we had a different strategy, which was pretty in itself.

Now having said that, there's no doubt that I wanted to participate directly in the cloning experiments. I didn't want to be a part of a process. However, I was unsuccessful. We had a real bifurcation of interests. Everything worked up to the point of the cloning per se. That situation was reflected in the authorship on the paper.¹ Despite my conversation with Chirgwin, we weren't concerned about noncompliance. Because I think we'd done what we agreed to do with Hans Stetten of the NIH. We'd talked about the situation internally; we'd made no effort whatsoever to control the internal discussion about the experiments with pBR322.

Hughes: The internal discussion within the NIH?

Rutter: Within UCSF. The only discussion to my knowledge that might have been public was through Hans Stetten to the NIH.²

Hughes: Because he was the only one you'd talked with about the pBR322 incident outside UCSF.

Rutter: And Hans Stetten either kept this to himself or talked to Don Fredrickson [NIH director]. I don't have any idea what he did then. And later when we discussed this matter with Don Fredrickson at the time of the Senate hearings, he didn't mention it, to my recollection.

Seeking a Source of Insulin

Rutter: Raymond Pictet did a beautiful job in developing methods of isolating islet cells and eliminating most of the exocrine pancreatic cells. That was extremely important because the

¹ A. Ullrich, J. Shine, J. Chirgwin, R. Pictet, E. Tischer, W. J. Rutter, H. M. Goodman. Rat insulin genes: construction of plasmids containing the coding sequences. Science 1977, 196:1313-1319.

²DeWitt "Hans" Stetten, Jr., was Deputy Director for Science, NIH, and chair of RAC.

exocrine cells were loaded with digestive enzymes, including enzymes that destroy RNA. Since we were after RNA, this became a very significant issue. It was the biggest downside to using islets. No matter how many islets were purified, there were always enough exocrine cells around to result in a high level of RNase. Nevertheless, eliminating most of the exocrine cells helped a lot.

Another point: RNase was one of the main issues, but the relative concentration of insulin cDNA to other cDNAs was also important. Thus the choice of pancreas with all its problems was better than tissue culture cells which had much lower relative concentration of insulin mRNA.

Hughes: I see.

Rutter: So Raymond's ability to develop a highly purified preparation of islets was absolutely critical. Luckily, the islets contained mostly B cells, cells in the heart of the islet. Around the external part of the islet, there are cells that produce glucagon and also somatostatin and another minor hormone, pancreatic polypeptide. I'm not sure whether it's the preponderance of islet-producing cells or the protease treatment which trims off some of these external cells which is most important, but the net result was that this preparation was greatly enriched in the mRNA for insulin.

Isolating the Insulin Message

Rutter: Now, with respect to the isolation of the message itself, there were standard methods for isolating RNA from tissues. They worked in the case of isolating hemoglobin mRNA because erythrocytes don't produce RNase. The hemoglobin mRNA is stable, a highly enriched source, and therefore cloning the hemoglobin cDNA was relatively straightforward, and the hemoglobin mRNA sequence. This is not true of course in the case of insulin, and in fact, in most other cases, the RNase concentration is significant. This applies to the other strategies that I've mentioned to you before, such as going to Texas in order to isolate islets from young beef cattle where the proportion of islets in the pancreas is increased.

Having failed with these other strategies, we focused on rat islets. There the elimination of RNase activity became the crucial step in the process. There were many methods that had been developed to reduce RNase activity. This is quite a

challenge: RNase is one of the most stable proteins known. I think I mentioned that it is stable to boiling, for example.

Hughes: Yes.

Rutter: So I must have mentioned that we tested all known methods without success. The RNA was largely destroyed. John Chirgwin went through these methods very deliberately. The question was whether very harsh denaturing agents such as guanidine hydrochloride could be used under some conditions. Guanidine is one of the best agents known to denature proteins--destroy protein structure. But guanidine by itself didn't work sufficiently. The RNA was still largely clipped. I became very concerned about the overall strategy. It was conceivable that we could not develop a method that would produce good RNA. If so, this strategy would have been fundamentally flawed.

I was concerned that even though John Chirgwin was a very bright fellow he wasn't aggressive in his experimental program.

Hughes: Were you thinking of the competitor [Walter Gilbert] across the continent?

Rutter: Sure, we were thinking about that. Competition was the major issue. But being successful at all was another concern. It would be terrible to get trapped on a problem that was insoluble. So we spent a lot of time discussing various alternatives. There was another class of agents, chaotropic agents, that effects protein structure not by charge, as in the case of guanidine, but essentially by changing the characteristics of the water and changing the internal hydrophobic structure of the proteins.

It occurred to us that we should try combinations of molecules that operated by fundamentally different mechanisms. A powerful chaotropic agent was thiocyanate. Of course, the fundamental question was the rate of denaturation--RNase operates instantaneously, therefore the agents must act even more rapidly. The results were surprisingly good.

I think John responded to the challenge very well. He focused his energies then very sharply on refining the method to something very practical. This method or slight variations of it is still the preferred method for isolating intact RNA.

Hughes: He came up with this dual approach?

Rutter: I believe that we came up with that in our conversation. I think I was the one who suggested it, although I wouldn't say that it was unique. I'd known about chaotropic agents because of an

interaction I had had with a group of people at Duke--Charles Tanford had worked on the theory of chaetotropic agents. But certainly John did the experimental work.

Howard Goodman and His Laboratory

Rutter: We had meetings during this time. Howard Goodman went on sabbatical in either the fall or on January 1, 1977. I could never understand how Howard could leave when things were so exciting and uncertain. There was no better place to do science or work on hot projects. But Howard loved to travel and do new things. He was constantly attempting new technical approaches. He decided on going on sabbatical to learn some new things. He was a tense guy during these times and he might not have had the best relationship at that time.

Hughes: Best relationship with whom?

Rutter: With people in his lab. I don't understand to this day why he decided to go. I've never talked to him about this. Of course his lab was involved in two major high profile projects [cloning the genes for insulin and growth hormone]. At the same time, he loved to do things by himself in the lab. His lab became too active to do his own experiments. At some level, he became a competitor of the people in his own lab for equipment, reagents, etcetera. I honestly believe this was a factor--he really wanted to do things himself. He loved personal science and therefore maybe going on a sabbatical allowed him to practice science by himself. But he remained in contact with the lab.

Of course, Axel and Seeburg and John Shine were all quite accomplished people technically and theoretically. The whole environment encouraged experimentation--doing what needed to be done. There was a good deal of interaction between the various labs. Similarly we were doing a lot of cloning on different subjects. Curiously, while Howard was on his sabbatical, Pablo Valenzuela in my lab ended up doing the same kind of experiment Howard was performing. We found introns for the first time in very small tRNAs. That was unusual because it was thought that introns were passively present on large genes. That they were present in some small genes that were less than a hundred nucleotides was truly extraordinary. At that time there was a mystery about the function of introns and so it was a major finding.

Also, while Howard was doing this in Ben Hall's laboratory, Pablo Valenzuela and some others were doing it in my lab, and we were publishing at exactly the same time. Very competitive situation.

Controversy over the Use of pBR322

Rutter: At any rate, back to the insulin story. Howard was in regular contact and planned to come back at fairly regular intervals to go over things. But the insulin project continued vigorously without him. Obviously, I was in general overlooking the project. But the cloning experiments had been negotiated prior to this. Axel Ullrich would do the cloning along with Edmund Tischer, who was a technician.

My office was down on the ninth floor in the East Tower, where Peter Walter now has his office. Of course, I was running the department. The office was also on the ninth floor and I had a large lab. In early January [1977], Axel came in and told me that he had just gotten a call, from Betty Kutter I believe. At any rate, he said he received notice that pBR322 had been approved. So I said, "Great. That's super news. Go for it." Starting whatever date that was--as I recall, it was the middle of January--he began using pBR322 and then, after a relatively short period of time, we got clones that were positive, again by testing via this cleavage method.

Hughes: Did you understand at that juncture the difference between approval and certification?

Rutter: There was no difference at that time. There was none. Approval by the committee was accompanied immediately by NIH endorsement. Up until this time, everybody acted on the votes of the committee. Certification was a concept that came suddenly, and without notice.

Hughes: But that becomes a bone of contention.

Rutter: Oh yes. Surely. Absolutely. It was the bone of contention between us and the NIH. We understood: it [pBR322] was approved--period. It was only later that certification became an issue.

Hughes: That's not quite the way Stephen Hall records it.¹

¹ Hall, pp. 116-117.

Rutter: Well, it's the way we understood it. It was only in February that the certification issue came up.

Hughes: What was supposed to happen between approval and certification?

Rutter: The RAC committee was advisory to the head of the NIH. It was the right of the head of NIH to take the final decision and responsibility.

Hughes: But certification was not more than a rubber stamping?

Rutter: That's right. The committee was the one with scientific input. The head of the NIH was supposed to certify the action of the committee for formal purposes, perhaps taking into account other issues.

Hughes: If that's the case, why did it take six months?¹

Rutter: Fundamentally, I don't know. Part of the time was due to a requirement for additional data to be provided by [Stanley] Falkow and perhaps others. This was apparently a move by NIH authorities to become more formalistic about the process of approval.

There were others, including scientists, that lobbied for more highly regulated control. Those who believed that recombinant DNA research was dangerous or should for whatever reason be under public scrutiny wanted to have laws administered by an agency. As this issue received more and more attention, there was a perceived need to develop more and more crippled vectors. Coincidentally, the approval process became much more complicated. It received more surveillance because it became a political issue. All this was happening during this period. It is obvious in hindsight, but not so clear during real time.

Up until this January [1977] meeting, everything had been recommended by the committee, NIH authorities were present, and approval occurred virtually simultaneously. But after the approval [of pBR322] by the committee, then we heard somehow it just needed to be signed by the head of the NIH, Don [Fredrickson], a formality. The approval and certification process was so coupled and so informal. To my knowledge, the approval process and the results were not announced formally, as in a press conference or through the scientific journals. It was done by telephone, I think, so people in Herb's lab and others who had an interest felt that everything was perfectly okay to use pBR322. I think it [NIH approval of pBR322] had been disseminated by Boyer to other scientific groups at UCSF. What happened at NIH after the committee action, I honestly don't know. In fact, I would like to know this aspect of the history. When it got to

¹pBR322 was certified for use on July 7, 1977. (Wade in Science, 1977.)

NIH, for one reason or another, another strategy for certification came on board.

Hughes: Because of this external pressure?

Rutter: I don't know, but perhaps the external pressure made them much more serious. This again was not communicated. When Axel got clones in early February--I could be wrong on dates; I am just terrible on dates--I think we had a meeting. The data showed that the clones had a fragmentation pattern that conformed to insulin--tremendously positive result for us. Then Howard came back from Japan.

During this period there was an ICN-UCLA meeting in Utah, a general meeting--scientific meetings in the wintertime were frequently held at ski resorts. During the meeting, William Gartland [RAC chairman] was asked which vectors were approved--pBR322 was not mentioned!

Hughes: As being certified?

Rutter: As being certified. Somebody asked from the audience, "Didn't you miss pBR322?" He said no, it hadn't been certified. One of the people from the lab, perhaps John Shine or Axel Ullrich--neither Howard nor I attended that meeting--called up and said pBR322 was not certified!

Hughes: Ullrich was at that meeting. According to Hall, so was Goodman.¹

Rutter: Could have been. I didn't think that Howard was at that meeting. Anyway, I know that I wasn't--I was in Texas at another meeting. Somebody reached me in Texas; I don't believe it was Howard--maybe someone from my lab? But I did talk to Howard, I think before I returned to San Francisco. When we returned--it was several days or a week or so later--we met. We had a terrible situation: we had insulin cDNA clones, and pBR322 was not certified!

On the one hand, everyone was laughing at the bureaucratic delays in certification of pBR322 because it was basically the same vector as pMB9 and was "safer" by the criteria than other approved vectors. The NIH certification process was considered to be politicized and not the result of a scientific evaluation since the committee itself had approved it.

Hughes: Which indeed was the case in this instance?

¹ Hall, p.123.

Rutter: To my knowledge there wasn't any additional scientific information required after formally receiving Falkow's data.

Hughes: So approval was on the basis of as complete a scientific picture as could be gathered.

Rutter: That's my understanding. Apparently during this period the process for NIH certification was bureaucratized. Of course, during this time, they were just beginning to set up the processes to be used by the Recombinant DNA Advisory Committee [RAC] and recruit the staff, etcetera. For one reason or another, pBR322 got delayed by the process. Of course, that gave us super consternation, so we had a meeting.

Hughes: Who's "we"?

Rutter: Howard and I probably, Axel, and maybe John Shine. I don't know if it was the whole team. But it was certain that we all anguished about this. Howard and I did most of the thinking about the next consequent steps to be taken.

Hughes: You were the two that presumably had to make the decision.

Rutter: Right. We were deliberating. One of the technicians in my lab, Jennifer Meek, talked to David Martin about this issue. David Martin was in the Department of Medicine. He was a molecular geneticist and a savvy person. The dean had put David Martin in charge of the local [biosafety] committee to approve recombinant DNA vectors. I of course told David what had happened, and immediately went to see Julius Krevans, the dean of the School of Medicine at the time. Howard wasn't involved in that part of it, but undoubtedly talked to them later.

We were concerned about alternatives and decided to record the possible actions we could take. A preliminary decision to keep the DNA was made (since there was no harm at this stage). This was memorialized in certified letters sent to each other to formalize this decision.

At the same time, I wanted to find out what the NIH's position was with respect to use of vectors which were noncertified under these conditions. So I called Hans Stetten, DeWitt Stetten, who was the scientific leader [Deputy Director for Science] at the NIH and a distinguished scientist in his own right. I tried to reach him over a couple of weeks.

Hughes: You called him because of his position at NIH?

Rutter: That's why I called him. I knew him as well. I called him and asked for his advice. I set up the case. I delicately broached the subject so that I felt we wouldn't compromise him, by asking what would in his view happen if somebody had specifically used a vector that had not been certified, believing it had been approved. Hans told me that this would be a disaster right now.

Hughes: Thinking of the political situation.

Rutter: Yes, it was the most intense period of political debate around this issue.

Hughes: It couldn't have happened at a worse time.

Rutter: It was terrible. So he said, "If this happens we'll have laws governing the science. There is no question that under these circumstances this will result in laws being passed in the United States. They will result in increased bureaucratic restraints on the use of recombinant DNA," and so on. He went on for fifteen minutes. I had more than one conversation--I think two--with Hans on this subject over a couple of weeks.

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Rutter: We were not overly concerned about the ethics of the case. We felt we had conformed to the guidelines as we understood them and therefore felt that we could publish this work directly. This was a serious alternative, probably in hindsight the preferred alternative. During this time interval, there was a lot of writing being done about using various alternative vectors that could be tried with this good cDNA prep. Howard did this while he was in Seattle--University of Washington, and perhaps while he was in Japan--in order to make sure that the paper could be completed when a successful cloning occurred.

Most of the write-up at that stage was done by Howard, and the people who were involved in the experiments contributed their experimental protocols and gave the data. I got involved in writing the introduction and discussion section, and helped to edit the final paper.

Hughes: The Science article.

Rutter: The Science article.

The Press Conference at UCSF, May 23, 1977¹

Rutter: I thought the Science article would be a nice article but I had no idea that its publication would engender as much public response. The idea of a press conference was totally surprising to me.

Hughes: Whose idea was that?

Rutter: It probably came from the publicity office here, probably Michela Reichman. Anyway, there was a press conference, and there the dean introduced us, and I introduced the subject. Then Howard talked about it. I think we both talked about it. In hindsight, we should have more broadly involved the scientists who had done the work.

Hughes: Had you prepared for this press conference?

Rutter: No. First of all, I had never held a press conference before on science matters. In fact, I had never been to a press conference before. I honestly didn't know what was involved and I wasn't prepared for it. Michela--I'm quite sure it was Michela--had made a nice illustration that described the sequence of the cDNA. There were TV cameras. We described the sequence of the insulin gene, and how it was related to the hormone itself, why insulin was relevant to diabetes, and what effect this might eventually have on the production of insulin. But the impact was much bigger than I had expected.

Hughes: You mean the public response?

Rutter: The public response was much bigger than I expected. If I had thought of it in those terms, I certainly would have been more aware of the attention to the vectors employed. Nevertheless, it happened.

Commercial Prospects

Rutter: On the very day that this paper came out, I was reminded recently, the chief scientist, Bruno Hansen, from Nordisk, a Danish institute which produced insulin, with Jens H. Nielsen visited our lab and discussed the possibility of using these clones to make insulin commercially. So there was an interest established almost immediately. However, it was a long way from the gene to a commercial process. Basically, as I said before, this was not the purpose of the work, and perhaps was questionable as a commercial

¹See the Time magazine article in the appendix.

project. But the cloning result was immediately projected in this direction.

Targeting Human Insulin

Rutter: After this result, we obviously wanted to get the human insulin cDNA as fast as possible and then carry out studies on its expression. At this point, we had a real tangle with Howard. In the end, we asserted that we were going to work on the cloning, he could also work on the cloning, and whoever got there first, got there. We would exchange information and reagents, but both labs were going to do the cloning. Obviously we would publish together.

Hughes: He didn't want you to get into cloning.

Rutter: No. There were lots of reasons, but for sure the issue of getting there and the issue of being a full partner were major concerns of mine. Also, quite frankly, I felt that the science was becoming too personalized. It was the first time I had experienced that people negotiated their authorship position before the work was done! I just thought there was too much ambition and driving for recognition when the work could easily be done by any member of the team at that point. Frankly, I thought the whole thing was being blown out of proportion to total scientific reality. This wasn't the first gene that had been cloned, for heaven's sake.

Hughes: But it was a very significant gene.

Rutter: It was a significant gene and it was a significant development, for sure. I was very happy about that. But put it in perspective, come on! There was no point in overblowing it. So probably I undervalued the achievement, and the people involved in the experiments overvalued it. At any rate, there was a lot of juggling for position.

I ended up bringing Graeme Bell into the insulin project. Graeme was a graduate student in my lab--great in the laboratory. He had worked on related technology before, but not on insulin. Howard from his side brought in Barbara Cordell who was a very good person as well. We began working in parallel on the human gene project.

Debate about Regulation of Recombinant DNA Research

Rutter: Then came the call by Nicholas Wade. Perhaps it was inevitable, but I absolutely could not believe my ears during these conversations. I spent many hours in conversation with Wade--ten, twenty, thirty, something like that. Intense conversation, picking over all of the details. I argued that it was not in the interest of anybody to write an article for Science about this.

Hughes: What was his response?

Rutter: Well, he listened, but he was going to write this article, no question. So finally I just tried to set the record as straight as I could. I tried to minimize the level of the conversation I had with DeWitt Stetten and any connection with the NIH because, of course, it would have been a real major issue if there had been disclosure of our discussions regarding the desirability of avoiding regulation by law.

I believed Hans Stetten and the NIH had given me the directions to minimize or downplay the pBR322 incident. In hindsight, I believe that the facts are the facts. History occurred more or less as it did. Each person had his own little part in it. However, there was and still is an interest and incentive to interpret and distort it, a kind of desire to rewrite history in terms of motivation or themes.¹ Wade and people like him blow up issues like this to make news and enflame public concern and in the end more intense regulation.

Hughes: What would be his interest in regulation?

Rutter: Of course, he didn't espouse this publicly, but I think he was one of the group who favored regulation. His actions suggest he had to be.

Clifford Grobstein, curiously and ironically, with whom I had done my work at Stanford on mesenchymal-epithelial interactions, was a very strong proponent of a regulatory agency. I believe he wanted to head the agency. Grobstein absolutely knew nothing about this technology, but was willing to regulate it nonetheless.

¹ Dr. Rutter is right about continuing interest. See, for example: Eliot Marshall. A bitter debate over insulin gene. Science 1997, 277:1028-1030.

The medical background, the microbiological background, the genetic background, the biochemical background were all areas in which Clifford and many people like him had no real knowledge. Those interested in regulation largely came from this group. In general they believed they were independent, unfettered by personal interest, and therefore better able to evaluate and regulate. I believed exactly the opposite; I believed that you had to know to be able to use wisely, and to regulate where necessary.

Hughes: How would you have done it?

Rutter: I felt that the Recombinant DNA Advisory Committee was a good approach. I supported it, given the circumstances. It was a lot better than having laws and formal regulation, with an agency to enforce and control processes. This would have been unprecedented in science, with the possible exception of nuclear weapons. I think history has shown that to be quite an acceptable way of dealing with things.

Senate Hearing on Recombinant DNA Technology, November 1977

Rutter: The [second] Senate hearing [of the Subcommittee on Science, Technology and Space] involved people from many backgrounds, appropriately. Herb was asked to testify.¹

Hughes: Why?

Rutter: The Senate was trying to get a general response from the university. The Senate hearings were, to some extent, directed toward the activities at UCSF.

Hughes: Yes, but what they were investigating was a supposed misuse of an uncertified vector, which Boyer hadn't used. Why Boyer and not Goodman?

Rutter: Well, because Boyer had developed the vector. He had applied to the committee for approval of the vector. He could have spoken with authority about the approval process. He had made all the applications. He was the right person to present that part of the story. It was appropriate for Howard to talk about the cloning, because the cloning occurred in his lab. On the other hand,

¹ For Herbert Boyer's account, see his oral history in the UCSF Biotechnology series.

Howard was on sabbatical, and I was nominally in charge of the [Goodman's] program.

Hughes: How did the invitation to appear before the Senate occur?

Rutter: I'm not sure. I think the invitation came to the university and then the university contacted the desired individuals. We talked it over. Howard said he didn't want to go. Under the circumstances, I said I would go. I think it was appropriate under the circumstances that I go to represent the lab and the department. It would have been better if all three of us had gone.

Hughes: How much did you know about what was going to be expected of you once you got there?

Rutter: I knew absolutely nothing! I talked on several occasions with [Senate] staff prior to the hearings. The staff was very agreeable. They were seeking information. They seemed supportive of our activities and our story. I was totally unprepared for what occurred at the hearings. So was Don Fredrickson of the NIH. We had met with Don Fredrickson just prior to the meeting, and also maybe the day before. We had coordinated our stories.

Hughes: What was he going to do?

Rutter: He was going to basically support our position.

Hughes: On what grounds?

Rutter: He knew that there was a difficulty with certification, etcetera, a major issue. I told him at that time quite privately of my conversations with Hans Stetten. I presumed he already knew about them, although I don't think that he admitted it. I told him that the main reason that we didn't disclose all of the details about the pBR322 incident was the concern about misinterpretation and the pejorative consequences to science. He agreed with the latter.

Hughes: Did you discuss why there had been such a delay in certification? Because he was responsible for that.

Rutter: He was clearly responsible for the delay. I didn't say, "Don, why did this happen? You put us in this mess."

Hughes: [laughter] I guess that would have been a mistake.

Rutter: He probably wouldn't say, "Well, it's all my fault. Let's blame it on me today." [laughter]

Hughes: That would have been nice for you. But that was a factor, wasn't it?

Rutter: It was the factor. But still, I didn't even think at that time, nor do I think today, of this alternative. He was subject to a tremendous amount of public interest and political pressure. He couldn't have done things correctly.

Hughes: Whatever he did.

Rutter: Whatever he did was going to be bad. We could wring our hands and complain about the situation but we were a captive of events. I believe that he had not experienced anything like this before and was also unprepared for it.

Anyway, what happened at the Senate hearings was totally amazing. There were rational individuals who were trying to understand and deal with the matter, like Barbara Culliton from Science. Others were trying to make a name--Nicholas Wade. Adlai Stevenson III also was trying to get votes and publicity, and the senator from New Mexico, Senator Schmitt, was a nuclear scientist who had previously worked in national defense.¹

Hughes: Ah, so that's where that comparison came in in terms of safety standards.

Rutter: That's where that comparison came in. He was by far the most creditable interrogator, because he understood the science approach. He was also the toughest on regulations. Clearly, from his background, he would have understood safety and regulation. Anybody who's been through the atomic bomb program knows what security is all about. His position was, there is no excuse for this kind of nonchalant, sloppy behavior. These guys from California don't know anything about handling danger. Probably he had plenty of experience with nuclear materials--really dangerous stuff.

The Cloning Race

Hughes: Plus you had a race going on to clone the insulin gene, which maybe was not of great concern to the folks at NIH but it must have been of concern to you.

¹ Stevenson and Schmitt were the senators presiding at the hearing.

Rutter: The race was made out to be tremendously more significant than it actually was.

Hughes: Really?

Rutter: Absolutely, in my mind at least. The notion was that there was a lot of money at stake or something like that. Therefore, the race took on an aspect beyond its scientific base. I absolutely don't believe that was the case. The fact that these experiments would start the biotechnology industry was not contemplated at that time. At least it was never discussed by any of us. The biotechnology industry seemed far in the future. If we had believed it was going to give us commercial and financial benefits, we would have paid more attention to patents.

Hughes: Yes, but aren't you putting too much emphasis on the money aspects? It seems to me that you get plenty competitive just on the science.

Rutter: Yes, I'm just trying to say that the discussions about these events were tinged with money, to enhance the competitive stakes beyond the scientific results themselves.

Hughes: I see. But just keeping it on scientific grounds, you were in a race.

Rutter: No doubt about that. There is no doubt that I am competitive, and there is no doubt that Howard is competitive as well.

Hughes: Right. So you didn't want to wait for six months or whatever it took to certify pBR322.

Rutter: Well, there is no doubt that we tried to deal with the situation as aggressively as we could. Nevertheless, as I said before, I also sensed that everybody wanted to do the right thing. So would we deliberately run a risk of essentially being castigated by the scientific community in order to be first in insulin gene cloning? The answer would be resoundingly, no! We were excited by getting the gene and studying the gene structure and its regulation. That was great. I would say the exhilaration of success was more related to the finding itself than to the competition. It's a lot more satisfying to write the paper yourself than to read somebody else's article. It's a hell of a lot better. In this game, one wants to write the papers; one doesn't want to read them.

You can relate that to the competition, for sure. But you can also relate it to the thrill of discovery. The two are widely misinterpreted--beating versus knowing first. The rush of knowing

first is tremendously more powerful than just the crass competition.

The Smithsonian Article and the NIH Guidelines

- Hughes: The Smithsonian article came out around this time,¹ which was directed to Boyer's lab, but it reinforced the idea of sloppy adherence to the NIH guidelines.
- Rutter: Yes. There was a woman in Boyer's lab--
- Hughes: Janet Hopson.
- Rutter: --who worked in his lab partly. And partly she appeared to be a mole.
- Hughes: That wasn't the feeling I got from the article. I think she was upfront about why she was there.
- Rutter: Well, yes. She was upfront about why she was there, but she was also perfectly willing to write a pejorative article without disclosing its contents prior to publication, and trying to influence the situation.
- Hughes: I thought she came with the idea of spending time in Boyer's lab to write an article.
- Rutter: Yes. I thought she was there to describe the science and the details of genetic engineering, not an article on attitudes, etcetera. In that sense she was a mole.
- Hughes: A mole to me means that nobody else knows why she's there.
- Rutter: Right. I didn't know she was there until after the article appeared.

The fact was, with everything going on, we absolutely made no attempt to control information. The philosophy that not only I espoused but we all espoused was openness. It would have been easy, very easy, to get information on any subject. For sure, there were different degrees of compliance to common standards. I

¹ Janet L. Hopson. Recombinant lab for DNA and my 95 days in it. Smithsonian 1977, 8:54-62.

think she got a view of the independent thinking of scientists in the United States, and probably in most of the world.

Hughes: I don't think we've made clear what we're talking about. Janet Hopson implied, or maybe more than implied, that adherence to the guidelines was taken in a rather lackadaisical fashion by certain members of Boyer's group, which was the only group she was observing.

Rutter: That's right. Also she specifically stated that procedures were not as carefully controlled as they might have been. I believe that her view accurately reflected the view of many scientists about the guidelines. I didn't know anybody personally who believed that the guidelines were justified on the grounds of safety. The guidelines were justified on the basis of policy and provided a rational means of dealing with political and social concerns.

Given that set of circumstances, there would be people who would laugh at them; others would take them very seriously. Clearly the department's view about this escalated tremendously. As soon as we became committed to compliance and security, then things took a totally different turn. I believe every laboratory in the United States--any laboratory anywhere had this problem. I dare say even the Manhattan Project in the early stages had a haphazard security system.

Hughes: Yes, I know it was.

Rutter: So after a while we learned how to interpret and follow the guidelines. We had a situation in which the standards of compliance were to some extent rigidly interpreted by the government, for example, people at the Senate hearing, and yet were just being devised and adopted by the scientific community. So it was a matter of education in these procedures.

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Rutter: But the implication that ambition, competition, and money drove illegal action was in my view fallacious.

Hughes: Could you dispel that notion?

Rutter: Not in that committee hearing. I don't know whether it's been effectively dispelled. The people who have experienced this situation in that period of time I believe still have differences of opinion. One can never dispel external views if these are coupled to a chain of significant events.

Weighing the Scientific Rewards

Rutter: Fifteen years later, we are still involved in patent hearings. There still are questions like, why was I elected [in 1984] to the National Academy [of Sciences]? Did this have to do with the insulin gene cloning? I say no, because the research which led to the election to the National Academy was based on work I did in the early 1970s. But the underlying implication was that I was elected under false pretenses.

Hughes: And implying that that might have even been your motivation?

Rutter: This might have been my motivation for deliberately carrying out non-approved experiments? Howard Goodman never was elected into the National Academy, or hasn't been so far. Considering membership in the National Academy as a measure of scientific contribution, in my view it's outrageous that he's not a member. He played an important role in the early days of genetic engineering! However, it illustrates the mixed views on the cloning of these genes. The papers on growth hormone and insulin genes and their expression were truly on the forefront of research in biotechnology. Whether this was at the forefront of science was a matter of debate.

Maybe the scientific establishment took a negative view of this work and therefore rejected Howard. I can't tell. The point that I'm trying to make is that the rewards at the scientific level for this work were not extraordinary.

Hughes: Would you put more value on the work that preceded it?

Rutter: No. I put more value on the work which succeeded it. The cloning of the gene and the use of the insulin gene allowed and facilitated the study of transcription and expression and the work on the insulin receptor and the mechanism of insulin action. This turned out to be a great story.

This is an analogous case to some degree to the David Baltimore case. A major scientist was accused of deliberate malfeasance. I guess you can see analogous trends. There was information bearing on this case [of the insulin gene cloning] that could have been heard, and concrete decisions made. But the case was still profoundly disruptive. It was the worst thing that ever happened to me in my life.

We didn't have a formal hearing on this subject. We did have a study. UCSF asked David Martin and his group [on the UCSF

Biosafety Committee] to carry out an analysis of this case and the procedures, and the NIH carried out an investigation.¹

Hughes: You mean by actually coming into the laboratory and watching what was going on?

Rutter: Not by watching. That would have been impossible. But the safety committee examined the issues.

Hughes: Were procedures changed as a result?

Rutter: The use of the P3 facility was carefully scrutinized, and the procedures were changed. There was no longer any argument about whether people obeyed the safety regulations or not. Regardless of their feelings one way or another, they were going to obey these guidelines.

This was also the beginning of the imposition of "laws", in this case "guidelines", which didn't have the force of a recognized basic validity. It was a response to a political position about which there was true argument. This was totally different from radioactivity. What had not been publicized was the difference between "hypothetical" risk and real risk. There have been many perceptive and important papers written on the evaluation of risk. What is a problem in legislation and in society in general is that the boundaries between real risks and hypothetical risks have been blurred, and the general population does not, in a sense, make a distinction between them.

This issue has cost society and science a tremendous amount of worry, time, and money. It continues to be a major issue in regulating scientific enquiry. It has increased the costs of doing science and decreased the enthusiasm for doing science. I would guess 10 to 25 percent of the total budget is now directed nonproductively. I am extremely unhappy about whatever role this incident at UCSF played in exacerbation of this trend.

Hughes: Yet there was a relaxation of the public concern about the potential hazard of recombinant DNA research, which was, to a certain extent, driving the regulative process.

Rutter: You're right. The public concern died when the first benefit became evident and the experience was positive. Clearly, at that

¹ See, for example: Minutes, Biosafety Committee, June 5, 1977; DeWitt Stetten, Jr. to David W. Martin, Jr., June 20, 1977. (Archives and Special Collections, UCSF Library, AR86-7, folder 76.)

time no one else was worried about it. So it was a creature of political ambition, that is to say, it was an issue that was manufactured.

Hughes: To what end?

Rutter: I believe that to some degree, some portion of scientists were genuinely concerned. Others enjoyed the debate and the public controversy. Some became public figures. For example, Jonathan King from MIT was one of those people. He was an articulate spokesman and a charismatic figure, but he presented an unbalanced point of view. George Wald, whom I had taken courses from at Harvard, was a Nobel Prize winner for his work on vision (rhodopsin), was a marvelous lecturer, and had made a great scientific contribution. But on this issue, he became a dangerous person. He emphasized the "dangers" without knowing or analyzing the details. He was so captivating that he could sway an audience by his personality and his articulation.

Hughes: And his scientific reputation.

Rutter: His scientific reputation extended far beyond the limits of his knowledge. The same thing with Margaret Mead. Didn't I tell you about her?

Hughes: No. [laughter] I haven't heard about Margaret.

Rutter: This was hilarious.

More on the Senate Hearing

Rutter: When we got to this [Senate] committee, beside Don Fredrickson and colleagues from the NIH, and Herb and me from UCSF, there were many witnesses and observers. Among them was Margaret Mead, who came wearing a huge long robe and with a long shepherd's staff. [laughter] She sat down right in the central part of the hall, which was wide but not deep.

The hearing was run as a legal hearing in a courtroom.

Hughes: Stevenson was a lawyer, was he not?

Rutter: Adlai Stevenson [III] was a lawyer. We were totally outmatched. Senator Stevenson ran the proceedings. Stevenson gave her this embellished introduction: "This great scientist, one of the greatest scientists who has lived..." After his introduction, he

introduced Margaret Mead as a world-renowned scientist who could give guidance on these issues. Here was a social anthropologist with her shepherd's staff giving her advice on molecular, microbiological, and physiological science. [laughter] She said something like, "You're going to hear today from these scientists that this is not dangerous. I'm here to tell you it is dangerous." After every significant statement she would pound the floor with her staff for emphasis. "These people are here, telling you it's safe. I'm telling you it's not safe." Boom! Boom! "These people are here telling you that they have only interests in promulgating the truth. Well, I'm telling you here, this is not the truth." Boom! Boom! Her entourage were there clapping after her significant remarks. Obviously it was a total setup, an amazing setup.

Hughes: Do you know how she had come to be there?

Rutter: Not to this day. She was, I think, part of a group of scientists that had a deep belief that working with DNA was counterproductive. Her husband...

Hughes: Which one?

Rutter: It was the one who was also a scientist and writer.

Hughes: Bateson.

Rutter: Yes, Bateson. Gregory Bateson was a little more eclectic with respect to science, but he still I think maintained a holistic, an anti-molecular approach.

Anyway, here was a distinguished scientist, albeit from a different field, setting the tone for a group of unknown upstart scientist who were doing "unusual" science, and who were accused of trying to become rich and famous. You can imagine the scenario. Everything was downhill from then on.

Don Fredrickson had previously consulted with me on our testimony. We agreed on the contents and his support. After this verbal attack, he immediately retreated. [He was asked:] "Why haven't you done this and this and this and this?" The questions made him look pretty bad. So the idea of supporting us totally disappeared. We became the scapegoats.

Hughes: So there you were.

Rutter: There we were, left hanging. Herb made a few comments on pBR322, which took a couple licks. But then they focused on insulin cloning. I guess we pretty much looked like schoolboys.

Hughes: Did you have any chance to regroup?

Rutter: No, not really.

Hughes: What had you been planning to do?

Rutter: You mean, for this hearing?

Hughes: Yes.

Rutter: We planned to discuss exactly what had happened. We had been led to believe that it was going to be a friendly discussion to exemplify the problems which we had to work through in order to clarify the issues, etc.

I wrote a blistering letter afterwards to Senators Stevenson and Schmitt, saying that we had been misled by members of the [Senate] staff and that I thought that Stevenson misinterpreted a number of significant issues.¹ It was to some extent a response to this hearing. There was a period of time when we didn't know what would result from this. The NIH had several possible actions. There was no threat of a suit or a danger of serious legal action. But they could have really made it difficult for us.

We had discussions with the UCSF staff afterwards about what we were to do and what our response was to this set of questions. Then perhaps as is typical of these hearings, as I understand it, they keep you hanging. They also don't do anything unless they have a concrete action.

Hughes: Did the letter represent a turning point? Would you have been censured if you hadn't written it?

Rutter: I don't know. I doubt it because I believe that they realized that when it came right down to it, the NIH's guidelines and their interpretations were not well developed. The NIH carried out an investigation (though not an extensive one) and concluded that the incident was understandable. They wrote a letter of apology for

¹ Dr. Rutter wrote a different letter to each senator and eventually received a response from Schmitt. No response from Stevenson was found. (William J. Rutter to Adlai E. Stevenson, November 22, 1977; William J. Rutter to Harrison H. Schmitt, November 23, 1977. Archives and Special Collections, UCSF Library, AR 86-7, carton 2, folder 82. Harrison Schmitt to William J. Rutter, January 10, 1978. Archives and Special Collections, UCSF Library, William J. Rutter papers, Mss 94-54, carton 2, folder 24.)

not communicating the guideline more clearly.¹ I mean, the NIH bureaucracy [RAC] was not set up. Any objective group of observers would have said we had been caught in an ambivalent situation.

I remember very well talking with Barbara Culliton about the issues. Barbara was on the editorial staff of Science and she realized what the issues were. I told her I wished she would write an article on this situation. I think that she felt that she couldn't, since Nicholas Wade had already written a report. She mentioned there was a kind of a division in Science, with a group of reporters who were the flamboyant type, and another group of editorial writers who were more conservative. The two didn't mix well. She was for, I think, a more sober discussion of the pluses and minuses of cloning and the effects the guidelines and regulations were having on the conduct of science.

On one side, we had the option of "going public" on this matter; becoming aggressive, or remaining passive. I remember after the initial press conference, I met with David Perlman of the San Francisco Chronicle. David asked about the cloning process, etcetera. I didn't mention the pMB9/pBR322 issue. (This happened before publishing this Science paper.) I've heard that David always felt that I didn't tell him the whole truth, so he was pissed off.

Hughes: I don't understand why you were keeping it from him.

Rutter: I don't understand why you don't understand. Because at that time this would have simply brought it all in the open. If we had wanted to discuss it, we would have published a letter or article in Science, not discuss it in the public press.

This was very difficult for me personally, but I still think I did the right thing, so I have a clear conscience about it. We don't have laws to regulate recombinant DNA research, and we have enough surveillance on these matters. If we had laws, we'd have progressively more constrained use of recombinant DNA methodology. Wherever you see regulations, you see a depression in the utilization of the science for technology, higher costs, longer timelines, more frustration.

Genetic engineering in the plant world has become ridiculous. Because of concerns, companies began to clothe their scientists [in space suits] in the field. This in turn engendered the response that it must be dangerous. So the situations became

¹ Dr. Rutter may be referring to the letter from Stetten cited above.

exacerbated in the public eye and in political domains. The risk/benefit assessment, especially for hypothetical risks, is one of the major issues facing our society and mankind itself. We caught the brunt of it in this case.

Translational Fidelity, Risk/Benefit, and Recombinant DNA Vaccines

Rutter: After that incident concerning pBR322, the Goodman laboratory and our laboratory became more directly competitive. I tried to be ecumenical but also I wanted to get on with science. I became interested in this risk/benefit issue since we had been "victims" of it. I reasoned that even though the genetic code was general, that the expression of the proteins, the translation of the genetic code, could be to some extent idiosyncratic in biological systems. Therefore, it might be that translation mechanisms in different systems might not have uniform high fidelity, that is, there could be translational errors. This became a significant issue for me.

I remember when I first described this possibility at a meeting in England. In the beginning there was little concern about this issue. But later it was recognized as important as the mechanisms were evaluated. For example, the tRNA [transfer RNA] concentrations vary dramatically in the same cell, as well as in different cells. Since the codon usage varies for different organisms, one could easily imagine that codon preponderance could result in an alteration of error frequency. That's when I began thinking of a problem which didn't require absolute fidelity. That's when I started considering vaccines. I became convinced that we should begin work on an expression program other than insulin.

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Rutter: After the insulin gene cloning, we were visited by many companies which had an interest in manufacturing insulin. This became interesting to me too! We talked with the Genentech group; they focused on the two-chain synthesis with Itakura and Riggs.¹ We favored the direct synthesis of proinsulin, followed by cloning the connecting peptide. After discussions, we finally ended up with a contract with Eli Lilly.

¹ For more on the synthetic DNA approach to insulin synthesis, see the oral histories in the UCSF Biotechnology Series with Herbert Boyer, and with Robert Swanson in The Bancroft Library Series.

Hughes: Why Lilly?

Rutter: Because it was a major insulin manufacturer and an American company. We thought it was simpler! [sighs]

About halfway into the collaboration, Howard became an independent consultant of Hoechst, which also made insulin. I disagreed with this conflict of interest--committing ourselves to a program with Lilly and yet being consultants to other companies. That was the beginning of a fundamental split between us.

Hepatitis B Vaccine

Rutter: In the fall of 1977, I talked to Roy Vagelos, who had been professor at Washington University of St. Louis and had recently gone to Merck as head of Merck, Sharpe, and Dohme. I asked his advice on the insulin deal. Since Merck was not involved in insulin, he was not conflicted. I also told him I was quite interested in developing a vaccine as a demonstration of benefit over risk, particularly because one didn't require complete fidelity in the translation system. Most molecules had to have the right antigenic structures, but not all of them.

Then Roy told me about their program with hepatitis B. I told him that I had worked as a consultant for Abbott Laboratories [1960-1975]. I'd worked there ever since I had been an assistant professor and had over time become a senior consultant. One of their programs had been in diagnostics. They'd developed a diagnostic test for hepatitis B, so I was familiar with hepatitis B and the unique aspects of that virus. It was a very short virus; its DNA was comprised of 3200 bases. So it was only three times the length of the insulin gene. It was the smallest known human virus, yet a major health problem. In short, it was a good problem and I knew about it.

It turned out that Merck already had an in-house program to make a hepatitis B vaccine with Baruch Blumberg, the discoverer of the virus who received the Nobel Prize for his work. Merck's vaccine candidate was from infections HBV [hepatitis B virus] particles found in blood of infected patients. This virus produces many particles that don't contain the DNA core, essentially particles comprised of the surface antigen. The vaccine was comprised of those isolated particles placed in Al_2O_3 [aluminum oxide] gel.

Hughes: Blumberg had done that?

Rutter: They were progressing along that strategy for a vaccine. However they also sold those antigens to Abbott for an HBV diagnostic test, which is something they weren't interested in commercializing themselves. Immediately, I suggested that we should develop a vaccine together. I thought there was a high probability that we could mimic that virus by producing those particles in a microbial system. Then there was no chance of having infectious viral particles in the vaccine. Roy became excited by the possibility.

I said, "I'd like to involve Howard Goodman in this." Then I came back to Howard and I proposed that we make a joint program together: "Let's work together more productively on insulin, and we'll do this hepatitis B vaccine together." He liked the idea and visited Merck, gave some seminars, and got acquainted with them. Although we shared the hepatitis program, I really drove the hepatitis program.

Hughes: Had anybody approached a vaccine in that manner?

Rutter: No. That was the first time a biologically engineered vaccine had received FDA approval. The second vaccine developed with recombinant technology is the pertussis (whooping cough) vaccine. It is just now coming out in Italy for children.

Hughes: That's interesting, but I really meant by using this surface antigen approach.

Rutter: You mean, are there other viruses that throw off such particles, just the surface antigen?

Hughes: Yes.

Rutter: No. That's the only one I know of, although there is always a subfraction of particles in viruses that are not infectious. They are called defective viruses. In the particular case of HBV, there was no DNA inside those surface antigen particles. They had a quite different size and could be separated from the infectious HBV virus by centrifugation. This was very unusual, and it was a terrific example of just the right thing to do, at the right time.

I wanted also to use this collaboration to get Howard to settle down and start working productively on this project and in the department. John Baxter and Howard were still working on growth hormone. Now we had some common interests, production in bacteria. We had the genes; now we had to produce them. That was a big race, too.

The Rat Insulin Gene Project: Context

[Interview 10: August 30, 1992] ##

Constructing Safe Vectors

Rutter: For the first part today, we are going to describe more fully the events surrounding the case of pBR322 in the spring of 1977, cloning the [rat] insulin chain, and the subsequent decision to destroy those clones and to reclone the insulin cDNA.

After we had adequate cDNA libraries prepared from pancreatic rat islets, we had to select the best cloning procedure to get clones to sequence in order to find one or more that encompassed the full cDNA. You will recall that after the Asilomar conference, there was a general agreement to use only vectors that had approved levels of safety. Eventually, an advisory committee of the NIH¹ was established to provide advice or to rule on the safety of the vectors and provide a central forum for discussion and evaluation of the vectors that could be used in experiments. The first approved vectors were extremely inefficient, not only from the standpoint of the ability to incorporate cloned DNA inserts into the vectors, but also inefficient in the ability to discriminate between clones that contained an insert and clones that did not.

Herb Boyer's laboratory had been one of the labs that focused very heavily on the development of improved vectors that were safer and also that displayed better discrimination between clones with inserts and those without. The early vectors used resistance markers against either tetracycline or colicin, a natural agent which destroys E. coli bacteria. The colicin screen was very difficult, and also the restriction sites in the vectors made the cloning process cumbersome. One selected for a change in the sensitivity to tetracycline or, better, an absolute change from resistance to nonresistance by virtue of insertion of a cDNA sequence. One employed these markers to distinguish between the clones that had inserts and those that didn't. This was critical because of the inefficiency of the sequencing techniques.

¹ The committee was subsequently named the Recombinant DNA Advisory Committee [RAC].

The development of the vectors essentially involved changing the resistance markers and simplifying the vectors by eliminating some of the DNA that contained unnecessary restriction sites. The safety issues concerned the ability of the vector to be mobilized by some process into normal E. coli strains instead of the crippled DNA strains developed specifically for the cloning process by Roy Curtiss, among others.

pBR322 was a major step forward in both "safety" and efficacy in the sense that it used tetracycline and also penicillin markers that could be used to screen with high efficiency. Further, these vectors were "safer" in that they were mobilized less well than other vectors, by a couple of orders of magnitude. We were very clearly awaiting [NIH] approval of this vector, along with all the rest of the scientific community.

Departmental Tensions

Rutter: In the middle of January 1977, Howard Goodman was in Japan. His laboratory was operating under the general supervision of Herbert Boyer, with whom he had been collaborating, and also Brian McCarthy. These gentlemen were not responsible for day-to-day experiments but in a general way they were available for consultation. This is the way laboratories operated during that time and, in fact, do so today.

Hughes: Each scientists had his own laboratory and was preoccupied with his own research?

Rutter: Of course. Each one had a large laboratory and many other responsibilities, so they weren't over there in Howard's lab working on collaborative projects. The same was true for me. I was also busy with departmental activities at that time. Gordon Tomkins's untimely death a few months before had thrown the department into disarray. I had to personally take the responsibility for Gordon Tomkins's continuing research activities. We adopted some of his people directly into my lab; others were more independent, and we set them up in their own lab.

Also there was the issue of recruiting a senior and very luminous scientist to replace Gordon and to add to the distinction of the department and continue to develop UCSF's image. So we were extremely busy and we had no one to take some of the administrative load. Gordon didn't take any administrative duties, per se, but he was, as I've said, a tremendously important, central figure in establishing the warm and cooperative environment in the department, and maintaining good relations with others, particularly the clinical departments. I could always depend on him to take much of the emotional load and, of course, after his death, the great esprit and cooperative attitude in the department was destabilized.

Hughes: Also, external tensions were escalating.

Rutter: That was obviously true because of the political and social issues surrounding cloning. The tensions on the outside were a big challenge.

Genentech at UCSF

Rutter: Quite obviously, there was also a major issue with the development of Genentech as a separate and in some ways competing organization.¹ I clearly supported the formation of Genentech and allowed it to set up its own laboratories at UCSF on the grounds that it was a useful experiment to establish a mechanism for technology transfer. In addition, it was clearly an adjunct method to support some of the research which was not so easily supported by NIH grants but was directly an outcome of the research that was being carried on in the department and elsewhere. It was a way to capitalize relatively rapidly on the scientific enterprise that we had set up here at UCSF, so everything seemed to fit.

However, it became complex in the sense that Genentech, and particularly Bob Swanson, began to run the Genentech group in a way that many thought was inappropriate for this environment. Many believed that Bob Swanson was "calling the shots" on the research being done. Secondly, there was, I think, a not very

¹ For the formation and early history of Genentech, see the oral histories in the UCSF Biotechnology Series with Herbert Boyer and with Robert Swanson in The Bancroft Library Series.

well disguised attempt to acquire the technology and programs in the rest of the department, without either giving credit to others at the personal level or giving credit to the university for much of that research. It wasn't clear at the time the degree to which there was commercial usurpation of the scientific technology that was being developed here. But it became clear afterwards that that was going on. I think some of the scientists were more acutely aware of it than others.

Hughes: Had the university administration entered into it directly at this point?

Rutter: The administration of the university and of UCSF were not worried about it, to my knowledge. That is one of the interesting things about medical schools; they are quasi-commercial organizations. There is an intersection with commercial organizations: testing drugs, developing or testing medical devices, etcetera. Traditionally, medical schools have been more interactive with industry because to some extent they had to be; it is part of their mission. Contracts for testing, contracts for clinical investigations, and so on, have traditionally been made between commercial organizations and universities.

However, premier universities pay close attention to the details of these matters because they don't want to be accused of being a commercial arm. Their interest is more in producing new scientific information and innovative clinical strategies. This is particularly the role of the basic science departments. Scientists are passionately interested in new information and technology they develop and of course naturally its value, both to other scientists and to any other group.

This is why there was a fair amount of contention about Genentech's operation as an extension of Herb Boyer's laboratory. Most of the people in Herb Boyer's laboratory were associated with Genentech. There were obviously groups within the department that were trying to do similar things. I mentioned that several of the groups were working on gene expression, for example, and if not ahead of the Genentech group, were at least competitive with it. They shared information.

Transference of Intellectual Property Rights to Genentech

Rutter: Some of the fundamental patents that Genentech finally ended up owning and using to their commercial advantage were based on work carried on at that time. The ideas were contemporary and I

believe were developed at UCSF. Of course, the academic labs were significantly disadvantaged over a commercial group because the commercial group could be more focused and bring more people and equipment to bear on these projects.

Hughes: Did Genentech have resources at that point?

Rutter: They certainly had resources, and they used their resources very well. In addition, Herbert Boyer had a good laboratory. And then Genentech got other laboratories to be involved, particularly Itakura and Riggs at the City of Hope. These laboratories indirectly were using personnel or information that was supported by NIH grants and other grants. The intellectual property rights were eventually transferred to Genentech. In principle, Genentech had a license to new technology prior to its publication. Further, it restricted the university's ability to license exclusively to others. In practice, the university did license technology exclusively, and eventually the governmental authorities, NIH, agreed to such exclusive licenses. So the net of all of this was the transfer of a great deal of scientific information to Genentech. I believe the university should have been generously rewarded by Genentech with royalties for their contributions. Patent disputes should have been settled.

Now, Herbert Boyer eventually gave all of the rights to the fundamental Boyer/Cohen patent to the Gordon Tomkins Fund of the university [UCSF]. Recently, this has been renamed the Boyer Fund. The royalties for the patents may be in the order of twenty-five to thirty million dollars, so in hindsight, the university was rewarded by Herb's generous contribution. On the other hand, the individuals that were associated with this work and the department per se were not recognized by royalties or equity in Genentech.

More on the pBR322 Episode

NIH Approval of pBR322

Rutter: At any rate, in the middle of January 1977, we were aggressively trying to produce the [rat insulin] cDNA and perform cloning experiments. The program was quite carefully negotiated. Axel Ullrich was in charge of the cloning experiments and Howard Goodman was in Japan. I, and of course the others in my lab, were very much interested in the experiments, but Axel had clear

responsibility for the execution. John Shine participated as a colleague by also contributing to the cloning methodologies.

Sometime in January, Ray Rodriguez in Boyer's lab received a telephone call from Elizabeth Kutter, who was on the NIH advisory board [on recombinant DNA research], which at that time was meeting in Florida. To the best of our knowledge today, Betty said that the advisory committee had approved pBR322. As late as December 1977, Betty confirmed in a telephone conversation to me that this was in fact the case. On the other hand, Betty was not willing to participate directly in the Senate hearings [on recombinant DNA, November 1977], so the evidence for the communication was not as clean as it should have been. Ray Rodriguez told me that Mary Betlach, who was a technician in Boyer's laboratory, somehow told Axel. At any rate, Axel came to tell me that pBR322 had been approved by the advisory board. I was in the office at the time, and I was extremely happy about the news and said, "Go for it", or something like that, and we chatted for a few minutes about the prospects with the new vector. Then I went on to do something else.

The P3 Laboratory

Rutter: In this time frame, we had also set up a P3 lab, and I had given Herb Boyer and Brian McCarthy the responsibility for looking over the procedures in the P3 lab. We had talked about setting up a logbook and operations of the P3 lab so that it could be used effectively by all members of the department, although logbooks were not required at the time. We thought it was the only way to restrict and record who used the P3 facility.

Hughes: Were you given any guidelines?

Rutter: Initially there were no published guidelines on the operation of the P3 facility. Eventually, there were guidelines on how the facility had to treat the safety issues. For example, there had to be an anteroom through which a person would enter, and the P3 facility had to contain all of the instruments that were required to carry out the experiment; you couldn't take materials in and

out. There had to be a mechanism to destroy the material after you carried out the experiment, and to remove the so-called waste from the experiment in a prescribed fashion. There had to be incubators inside the P3 facility so that you could carry out the incubation experiments. It was really a laboratory for containment.

Hughes: RAC had established those rules?

Rutter: Well, this was before there was a formally constituted RAC, but there was an advisory group. I believe that Bill Gartland had been chosen to head that committee and the advisory board, and the relationship of the committee to the NIH was just at that time being established. I am not sure when all of those things were determined, but I think that they were more or less determined by relating the requirements to previously delineated requirements for containment labs which were used for handling dangerous infectious agents.

Hughes: There was mention of Fort Detrick in Maryland.

Rutter: That was a P4 lab, which was another step up in containment. There were air locks, usually with showers, and one had to carry out experiments in glove boxes or in isolation. A P3 facility was a step down in security.

There wasn't any confusion about what had to be in the P3, to my knowledge. We consulted people within the NIH or elsewhere who had experience with containment in order to make sure our P3 facility was adequate. I think it was the first P3 facility set up in the United States for the purpose of cloning. I remember that there weren't any funds available for setting up a P3 facility, so I had to scurry around to get the resources to set it up.

The UCSF Biosafety Committee

Hughes: Did you have dealings with the biosafety committee here at UCSF?

Rutter: Yes, there was a biosafety committee, but it was primarily, as I remember it, devoted to evaluating clinical studies. The committee was reoriented during that period to handle DNA procedures and other aspects of biological/biochemical safety which were a concern on campus. In the department, Herb Boyer and Brian McCarthy took responsibility for the P3 facility.

Delay in pBR322 Certification

Rutter: During the interval between the middle of January and the first of February [1977], the initial cloning experiments occurred. I believe during this time period the first evidence of an insulin clone was obtained. If I remember correctly, on February 4, Herb Boyer mentioned casually that there was a delay in pBR322 certification by the NIH group, and that Don Fredrickson [NIH director] was waiting to get some data that was supposed to be presented to him by Ed Adelberg from Yale. This would inevitably delay the certification a few days. Cloning shouldn't be done in pBR322 at that time.

Hughes: Had you been aware that there was a two-step procedure for vector approval and certification?

Rutter: No. I certainly had not known about a two-step procedure. I assumed that there was single-step approval cycle. People on the committee itself and Herb only became aware of this process during that time period. However, this information was not transmitted broadly to the members of this group. This was the first time that there wasn't immediate approval of all the proposals brought before the committee. Even then the circumstances were to some extent informal in the sense that there was a process which one had to go through, but approval was virtually certain. I believe that Axel was not present when Herb Boyer mentioned that the vector was not certified¹, but he undoubtedly found out soon. Nevertheless, the cloning experiments had been performed.

¹ Hall maintains that "according to a later account of the meeting," both Axel Ullrich and John Shine attended the meeting on February 4, 1977. (Hall, p. 122.)

Sufficient material was available for sequencing, so sequencing was carried out. Later, in February or early March, there was a scientific meeting in Utah. In response to a question from the audience, Bill Gartland mentioned that pBR322 was not yet certified. It was at that time that Howard became acutely aware of the situation; he immediately flew back from Japan, had a meeting with members of his laboratory, and decided to halt any experiments with pBR322. He informed Axel who was still in Utah, and called me in Houston, Texas, where I was giving some talks. Of course I was shocked as well. I immediately flew back to San Francisco, and then we had a conversation about alternatives. Clearly, a number of cloning experiments had been carried out on growth hormone and insulin.

There was an issue in the early part of March about the lack of formality in using the logbook. I think the February 4 date was the formal opening of the P3 facilities, with accompanying rules for its use.¹ But in March, someone retroactively entered cloning experiments that had been done on February 4.

Hughes: Was that the explanation for the charge of retroactive entry?

Rutter: Yes, that was the explanation. The question is, why didn't the person enter the pBR322 cloning experiment at that point? In my view, the experimental results should have been entered, but they were not. With the retroactive entry of some of the experiments, including experiments with pCR1, another vector, it was clear that attempts to carry out cloning with the cDNA preparations, but with other vectors, were made during this time period. They may have been carried out in parallel all of the time.

Hughes: Do you know that because of the entries?

Rutter: Well, we know that because had they been successful, we would immediately have been informed.

Hughes: The fact that the attempt was made you got from the lab record?

Rutter: Yes, from the lab record and also later from the notebooks.

¹ According to Wade, the P3 lab "officially opened" on November 9, 1976. Wade in Science 1977.

When we came back from Texas and began discussing this, the question was, when was pBR322 going to be certified? Second, what responsibility did we have to report the pBR322 experiment? Third, what were we going to do with those clones? So at one level, there were telephone calls made to Bill Gartland at the NIH asking, "What is going on?" I made some of those calls myself; I know Howard did, and probably others did as well. As it turned out, they were setting up procedures themselves, and to our dismay, things were going glacially. Ed Adelberg was tardy in presenting the data that was necessary for the pBR322 certification.

Hughes: Why was he late?

Rutter: I don't know. He was providing some evidence from his own work that dealt with the safety of pBR322. He didn't develop this vector, but there were some issues associated with the use of the plasmid and its ability to be transferred from one cell to another and recombine with other plasmids.

Hughes: Was he having problems?

Rutter: I don't know; he just didn't get it done. He wasn't having problems; it was just a matter of organizing the data, presenting it to the committee, and probably they were setting up procedures. Later, they admitted that this was not an easy transition. Communications were poor. We have letters supporting the fact that it was a confused situation at the NIH.

I determined that we had to have some conversations at a different level, so I called DeWitt Stetten, the NIH scientific director during this period. I remember the conversation, "Hans, do you know that the guidelines are very hard to follow and there isn't good communication? In particular, the delaying action on this last set of vectors was totally confusing." There was a meeting of the advisory committee in March, and there was still another delay in the approval of pBR322. Given these facts, that is, since there was a two-month hiatus, we didn't know when it was going to be approved. Therefore, the pBR322 experiments became an urgent issue.

Hughes: Don't you mean "certified"?

Rutter: Excuse me, when it was going to be certified by Fredrickson's office.

Hughes: Did you call Fredrickson at that juncture?

Rutter: No, I talked to Stetten only. Stetten was the deputy director of NIH and scientific advisor and more directly connected with the experiments. I didn't know Don Fredrickson at the time.

Weighing Alternatives

Rutter: So we did two things. We asked an attorney, Lorrie [Lorance L.] Greenlee, who knew the technology, to give us some advice on what to do. Secondly, we thought about all of the alternatives ourselves, to decide what was best under the circumstances. As a result of the discussions with Lorrie Greenlee, we dictated a memorandum dealing with "matters of fact", and "matters of interpretation." The "matters of fact" section simply recorded what had happened, and "matters of interpretation" dealt with protocol.

We described the various alternatives after describing what had happened: should we report the pBR322 incident? Should we destroy the DNA? Should we keep the DNA? Should we transfer the genes to an approved vector? At the end of this, we came to the conclusion that whatever damage had been done, had been done. So what we were going to do was use the DNA. We came to the decision to write a paper on the experiment. At first, we thought this was the middle of the month, but a reconstruction of the time recently has indicated this was the end of March. We worked together on this record. According to Lorrie Greenlee's advice, I was going to send several copies to Seattle; Howard was going to mail me a copy and mail Lorrie Greenlee another copy.

Contacting DeWitt "Hans" Stetten, Jr.

Rutter: After Howard left, I finally got in touch with Stetten. I believe that I talked to him twice, but it could be that all of this occurred in one conversation. I revealed the fact of the pBR322 incident obliquely by telling him about a hypothetical situation: what would happen if someone carried out an experiment

with the unapproved vectors? Should one report the incident to the NIH?

Hughes: He knew that you were referring to your own case?

Rutter: There is no question about it. I told him that men of good will were confused by the guidelines at that time. Hans said, "My God, if this happens, we are certain to have legislation which would restrict the development of the whole field. This would be a unique thing in science and would be terrible for the United States."

Hughes: Had legislation been considered at that point?

Rutter: It was discussed very broadly at the time.¹ Of course, Hans was close to this, and he mentioned the hysteria that was associated with the issue. I remember he was fascinated that in France they were not at all concerned about the DNA experiments, but they were intensely concerned about fetal experiments, while we were concerned about DNA experiments. So the hysteria obviously depended on the press and the predilections of the society at the time.

All of this was to emphasize what a terrible thing it would be if these experiments were to be reported. So I asked Hans to think very carefully about what should happen under these circumstances. I went over the various possibilities. Stetten had no concerns whatsoever about the cloning experiments themselves. He realized the vectors were "safe". It was not an issue of doing a risky, totally unsafe experiment; the new vectors were better than the older ones; they had already been approved by the committee of scientific experts. He conjectured that, since the cloning experiments had already been done, transferring [cloned DNA] to another vector would have been possible. On the other hand, the transfer would have to be reported, and therefore the initial cloning would also of necessity be reportable.

So at the end Stetten thought that the investigators had a choice, but that the conservative way to handle this was to destroy the pBR322 clones and to essentially redo the experiments in an approved vector. Prior to this discussion, we had elected to use the cDNA in one way or another, at least not to destroy it.

¹ Federal, state, and local legislation to regulate recombinant DNA research was being discussed. See, Susan Wright. Molecular Politics: Developing American and British Regulatory Policy for Genetic Engineering. Chicago: University of Chicago Press, 1994.

We were going to freeze it as evidence that the cloning had been done.

Hughes: Who made that decision?

Rutter: Both Howard and I individually and the whole team collectively. I remember that everybody associated with cloning experiments got together, Axel and John Shine, for sure, and Howard and I. We also talked to Lorrie Greenlee.

The issue had come up whether one could patent a clone that was derived from the pBR322 experiment that was not certified. It was scientific information after all. I think that Lorrie believed that it was possible, but it would be challenged. Whether they would eventually allow it was questionable. Greenlee was a young patent attorney at that time and was well known to Howard. He actually went to law school with my son [William Henry Rutter]. He had previously been a professor at Caltech and decided in the middle of his career to change to law.

Hughes: Professor of science?

Rutter: Biological sciences.

Hughes: So he knew the field?

Rutter: To some degree. That was one of the reasons we had contacted Lorrie.

Agreement to Destroy the Clones

Rutter: After Stetten's call, I had a meeting with Axel Ullrich and John Shine and presented Hans Stetten's views. He very definitely believed that the most conservative way to deal with the matter, the least likely to engender a huge public reaction, was to destroy the clones.

Hughes: What was their reaction?

Rutter: They--and I--had mixed feelings. Clearly, this was a marvelous, even historical, result. They were disinclined to lose the valuable information and the clone. However, I remember eventually Axel agreed that we should destroy the clones. We talked about how to do it; agreed on using acid, which destroys DNA. He agreed to do it.

Hughes: He did it alone?

Rutter: He did it--he and John Shine. I think he wanted to do this himself, to take full responsibility.

Understand, at that time there was no easy way for me or anyone else to tell if you had destroyed clones. The only person who could have destroyed everything was Axel. There is no way to tell when you have a clone in a test tube; it is a clear liquid. It would very easily have been possible to keep some DNA on the side, while destroying some. What you had to do in a circumstance like that is fundamentally agree on the concept and trust the individual to carry it out.

Hughes: Was John Shine present when the destruction occurred?

Rutter: I believe so. I was informed after it was done. I remember clearly asking whether I should be there when they destroyed the clones. It was immediately obvious that that was stupid. I could witness putting acid in the tubes but this could mean that the clones were destroyed or not destroyed. In fact, we talked about having a little ceremony and decided that there was no point in making a big formality of it. Axel said that he destroyed the clones on the 19th of March, which was a Saturday.

On April 21, that is two days after the cloning, records show that Howard Goodman had a conversation with Stan Falkow. Falkow was a member of the rDNA Advisory Committee, and Falkow said, "Label the DNA and continue to do the experiments." I don't remember whether Goodman at that time had been in contact with us--he was in Seattle--but he certainly had not been available during this period and may not have known that Axel had destroyed the clones.

Going After the Human Insulin Gene

The Synthetic DNA Approach

Rutter: Meanwhile, in the same time frame, Howard, Axel, and John Shine had had conversations with Herbert Boyer about carrying out some experiments to get the human gene by mutating the rat gene. This required the use of synthetic DNA. There were only a few places in the country that could synthesize DNAs that would be long enough to carry out such an experiment.

The proposal was made by Keiichi Itakura, a scientist at the City of Hope, who did have such synthetic capabilities. It was a very interesting and challenging idea. This involved Art Riggs, another good scientist. Both were affiliated with Genentech; this was a Genentech experiment. Bob Swanson had presumably focused on insulin as a primary target for Genentech.¹

I recall that earlier on when Herb discussed possible targets for a recombinant DNA experiment, we mentioned insulin and glucagon. But the problem was the difficulty in synthesizing the genes. Glucagon was the first one [gene] synthesized because it was smaller.² Insulin was very challenging but nevertheless was a possibility. We talked about the difficulties in synthesizing the DNA as compared to isolating the genes by cloning.

Unbeknownst to me at the time, Goodman, John Shine, and Axel Ullrich signed a contract with Genentech that gave Howard in particular about three percent of the Genentech stock, and Axel and John Shine a substantial amount of Genentech stock and a moderate consulting fee. I don't know what it was--\$6,000 a year, \$10,000; something like that. However, this deal was conditional upon providing the clones to Genentech.

Debating a UCSF-Genentech Collaboration

Rutter: On the 21st of March, Goodman came to San Francisco. We were supposed to have a meeting, including me, at a restaurant on West Portal, a few blocks away [from UCSF], with the Genentech people, including Boyer, about a possible collaboration. In fact, Boyer knew about the sequence of the clones.

Sometime during this time period, either in April [1977] or perhaps later--I always thought later--Howard approached me with the idea that he would like to work with Genentech. I was not involved. This would be a separate scientific foray for him, and the theme of the collaboration was the modification of rat to human insulin. I did not disagree with his right to carry out the collaboration, but I was against using university materials to provide Genentech with a commercial advantage. So I told Howard that if he were going to go ahead with this, he had to get

¹ For details, see the oral history in The Bancroft Library Series with Robert Swanson.

²Genentech first synthesized the gene for somatostatin.

approval from the dean or the chancellor, but that I would have nothing to do with it.

Afterwards, I thought it better if both groups worked together on this project. So later, we talked to Genentech about both of us joining Genentech under circumstances that would give the university royalties from the insulin work. Indeed, we had dinner with the Kleiner-Perkins venture capital group at the Fleur de Lys restaurant. However, nothing came of it. Bob Swanson simply could not come to terms with Howard.

Hughes: Goodman didn't approach the dean or the chancellor?

Rutter: To my knowledge, no, at least there is no record of that, and I don't remember his having done that. I don't remember either of those two folks approaching me about such an arrangement. But there was considerable discussion between Howard and Genentech about sequence information and description of the gene. Furthermore, Howard also made a trip to Eli Lilly at the time, describing the fact that he had cloned the insulin gene, but wouldn't give them any details. As I remember it, all this occurred prior to the time that we decided to destroy the clones after the Stetten conversation.

The Rat Insulin Gene Project (continued)

Obtaining Clones and Sequence Data with a Certified Vector

Rutter: It became clear that the pBR322 clones were sequenced during this interval--February to March [1977]--and those sequences showed definitely that the clones encoded insulin. Sometime during this time, the vector pMB9 was certified for cloning.¹ This was a better vector than pSC101, but still it had a TET sequence that is difficult to use for screening.

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Rutter: pMB9 was more difficult than pBR322, but nevertheless Axel continued aggressively to obtain clones from the same cDNA preparation. It was evident from the early experiments with pBR322 that the quality of the cDNA preparation was exceedingly high because the proportion of clones that had insulin sequences

¹ pMB9 was certified on April 18, 1977. (Wade in Science.)

in them was very high. If any clones were obtained, the probability of clones encoding insulin was high.

Two types of cloning experiments were carried out: one in which we used the entire untreated preparation for cloning, and the other in which the cDNA was clipped untreated with restriction enzyme. Four types of clones were obtained, both with pMB9 and with pBR322. One represented long fragments of the cDNA and the other two were restriction fragments of the same cDNA, as well as a fragment of the second insulin gene, insulin II. The restriction fragment contained the three-prime end of cDNA and also had a run of T's which were complementary to the A's which are present at the three-prime terminus of the mRNA [messenger RNA].

As presented in the insulin paper,¹ there were precisely twenty T's on the restriction fragment, whereas the number of T's on the full cDNA was estimated to be about 100, but the precise number was not determined. On reflection, we thought it wasn't surprising that the clones would be identical, because if you cleave with the restriction enzymes, you would get the same sequence in a clone if there were no errors in reverse transcription. On the other hand, you wouldn't necessarily have the same number of A's because these would be variable.

What was remarkable in the cloning with pMB9 was the rapidity of getting sequences and the fact that the sequences were virtually identical, including the number of T's at the end. Logically, one would ask the question, well, why would you get the same number of A's? The probability of getting the same number of A's is small. In the case of the larger cDNA sequence, why would the five-prime terminus be identical? The five-prime terminus is determined by the ability to clip the hairpin at the end with an enzyme. So there is always a finite probability that you clip it in exactly the same spot that is determined by the structure of the hairpin and the ability of the S1 enzyme to cleave. The twenty three-prime T's were precisely the same. The only explanation I have is that one does not ordinarily carefully count T stretches.

¹ A. Ullrich, J. Shine, et al. Rat insulin genes: construction of plasmids containing the coding sequences. Science 1977, 196:1313-1319.

Writing the Paper while Research Was in Progress

Rutter: What happened after the pBR322 cloning and sequence information is that our group was so concerned about competition from Gilbert that we encouraged Howard Goodman and Axel to begin writing their part of the paper. So, in fact, several versions of the paper have been found. One of them includes pBR322 data, another one was altered for pCR1--and no clones for pCR1 ever were found--and another for pMB9.

The difference of openness in this matter is surprising. One group of people in the laboratory said, "Shift the clones to another vector, report it as being cloned in the second vector, and forget about it." That alternative was presented when Howard initially discussed this with his laboratory. There were other people in the laboratory who said, "This is outrageous! And we are not going to have anything to do with it." Among those was a person named Betty Craig who had been in Howard's laboratory but subsequently shifted to Brian McCarthy's lab. Betty was very much against the cloning project; she didn't like the atmosphere in Howard's lab. Craig is currently a professor in Wisconsin and has testified on the other side of the cloning issue. Wes Brown, who was working on mitochondrial DNA, also gave counsel against transferring the cDNA from pBR322 to pCR1.

The manuscript that had pCR1 as the vector probably came from this approach [writing while the research progressed]. Howard had written different versions as models, first with pBR322 and then with pCR1, not knowing that it wouldn't be pCR1. By the way, pCR1 is indicated in the logbook, but there is no evidence of cloning success with pCR1. Nevertheless, this manuscript was used as evidence that there was an ongoing attempt simply to move the cDNA from one vector to another. Then finally, there was the data with pMB9, and much of the writeup was the same as in the manuscript with pBR322 and pCR1. We agreed that each one of us would write up a part of the manuscript. Of course, I was responsible, with others in my lab, for writing up the preparation of the cDNA and the background, etcetera, and Howard and his group would write the other part.

Hughes: Was this a typical approach to writing a paper?

Rutter: It wasn't typical; it wasn't atypical, either. Some people totally write their papers before they do the experiments. Excellent scientists who are very organized do that in order to conceptualize the experiments prior to their execution.

Hughes: I hope they later change the paper to reflect the executed experiments.

Rutter: Whenever one does that, naturally one runs the risk of not rewriting the paper to fully cover the results.

Hughes: Do you routinely pre-write papers?

Rutter: Not me. [However,] there have been times when there was a race-- for example, with hepatitis--when we pre-wrote the paper while the data was coming in. We knew we had clones and that the sequence was there. We totally pre-wrote most of the paper.

Trying to Keep the Experiments Quiet

Rutter: Back to insulin. As soon as the data became available for pMB9, we immediately incorporated them in our pre-written paper and communicated it. It was published the early part of May [1977]. Because of the discussions with Hans Stetten about the use of pBR322, we realized there was no possibility of either "covering it up" or "not covering it up". We certainly didn't want to advertise the happening because of the publicity and the likelihood of legislative regulation of the field. On the other hand, there was no possibility of our maintaining that this didn't happen. Under the circumstances, we decided to keep things quiet to the degree that was possible. Those people who knew about it, knew about it.

There was a fairly definite change in attitude during this time, that is, the experiments were not discussed. Betty Craig and others realized that nobody was talking about them. This was deliberate. We didn't want to talk about the pBR322 data; we wanted to get on with the cloning experiments in other vectors.

Hughes: There was criticism of the fact that there was no mention of the controversy in your paper in Science.¹ Was it appropriate to mention the controversy?

Rutter: Absolutely. It was not only appropriate but ordinarily there is no question we would have reported it. However, it was precisely because of Hans Stetten's advice that we didn't report it. If we had reported it, it would have naturally been discussed broadly at the NIH and would have become an issue. So if we were going to

¹ Wade in Science.

report this in a scientific publication, we either had to suppress the pBR experiments or we had to formally report [use of pBR322] to the NIH.

Later in the year, because of great interest in what was going on with the insulin cloning experiments and everything else that was going on at UCSF, there was considerable tension, and Nicholas Wade got word of this. I think I mentioned earlier that I spent a huge amount of time trying to convince him that the story itself wasn't worth the effect it would cause.

Alerting the UCSF Biosafety Committee

Rutter: In May [1977], long before Wade knew, we were trying to keep it quiet without reporting it formally to the biosafety committee [at UCSF] because that committee might have felt they needed to make a formal report to the NIH. But a person in my lab, Jennifer Meek, a friend of Leslie Spector's and a technician, told David Martin. David Martin then came to ask me about it.

Hughes: David Martin, as I remember, was head of the biosafety committee.¹

Rutter: He was, I believe, head of the biosafety committee at that time. I told him everything and the reasons why we were acting as we did. He understood the concept. Then I went down and talked to Dean Krevans, first alone, and then afterwards with David Martin, explaining to him the whole situation.

Hughes: What was his reaction?

Rutter: The dean or David's?

Hughes: Both.

Rutter: David considered the problem just for what it was. He wanted to find the facts of the case. I told him he should obviously talk to Axel and John Shine and go through the whole process and get the views of all who knew or were involved. Julie Krevans was, I think, very understanding. He treated it as a problem to deal with matter-of-factly. Placed in the context of what had

¹ Martin was appointed chairman of the biosafety committee when it was established in the summer of 1976. (Leslie L. Bennett to David W. Martin, June 15, 1976. News Services Records, AR86-7, carton 2, folder 76, Special collections, UCSF Library.)

happened, he was neither surprised nor overly dismayed. He appeared to understand how it happened; he knew enough about what was going on in the field to place it in context.

Hughes: Was he also concerned about the implications for potential legislation if this information got out?

Rutter: Julie was broadly concerned, but not in a way that a scientist would have been concerned. He was certainly sensitive to the fact that UCSF would be the central focus of discussion, and that this would have disastrous effect on science. He saw the key issues very clearly. We then talked about dealing with the issues ahead. During this period, David Martin went on a sabbatical, and Jim Cleaver took over as head of the biosafety committee. Cleaver, along with others, carried out what I believe was a thorough investigation of all the individuals involved--not just the principals--and the biosafety committee reported to the NIH what happened.

Hughes: What was the time frame?

Rutter: I believe the June to July to August time frame; I am not sure about the dates.¹

More on the Senate Hearing, November 1977

Rutter: After the Nicholas Wade article, why we got the letter from Adlai Stevenson's staff asking us to discuss before the committee the difficulties that the labs had in understanding what the regulations were and in general in implementing them.

The pBR322 incident seemed a minor factor in their deliberations. In fact, most of the people who testified were

¹ According to a letter from DeWitt Stetten, Martin informed him of the pBR322 episode in a June 3, 1977 letter. (Stetten to David W. Martin, Jr., June 20, 1977. News Services Records, AR86-7, carton 2, folder 76, Special Collections, UCSF Library.)

interested in recombinant DNA research. Paul Berg, who obviously was a key scientist in this field,¹ testified on the general issues, but also Clifford Grobstein testified. Clifford Grobstein was an embryologist who had never done a recombinant DNA experiment in his life. (I had taken a sabbatical in his lab fifteen years earlier.) I told you that Margaret Mead seemed to get the most attention.

In the context of the hearing they--the Adlai Stevenson-Harrison Schmitt committee--gave no indication that the pBR322 incident was going to be featured or even dealt with more than peripherally. We were prepared to acknowledge the problems as exemplified by this incident, but also testified that people were, by that time, committed to obeying the guidelines.

Hughes: You presumably went to the hearing with the perception that there was concern about the supposed violation. You must not have thought that you were just presenting evidence to help with implementing the guidelines.

Rutter: No, perhaps naively, but certainly we were led by the Senate committee staff to believe that the hearing would not intensively focus on this issue. I wasn't at all prepared for a point-by-point discussion of what had happened. In fact, in discussing who should go to the hearing, it was believed that I should deal with the general issues. Howard should certainly have dealt with the specifics of the pBR322 incident. The university suggested that Herb and I should go, but did not insist on Howard's presence. I think this was, in hindsight, a big mistake.

During the interval prior to the hearings, there had been a tremendous effort to investigate everything associated with these events. No one had, I think, looked at the details as carefully as these staff attorneys, and they analyzed all the data carefully and knew the details of the plasmids pBR322 and pMB9, etcetera. I didn't know some details, for example, that most of the cDNA sequences had been determined from pBR322 in the February and March time frame. I thought that most of those sequences came solely from the pMB9 cloning.

Prior to that hearing, we met with Don Fredrickson and someone else, not Hans Stetten.

Hughes: "We" being you and Boyer?

¹ See the oral history in The Bancroft Library Series with Paul Berg, who played a prominent role in recombinant DNA science and the ensuing controversy.

Rutter: I don't believe Herb was there. Don had a deputy with him. I wasn't sure whether Don knew about my prior discussions with Hans Stetten, so I went through the discussions I had had with Hans Stetten. We agreed that I wouldn't mention those in the hearing.

Hughes: You and Fredrickson?

Rutter: Yes. We met I think for an hour beforehand, exchanging information. There weren't any substantial differences in our understanding of the facts on pBR322 and the situation which existed during the early implementation of the guidelines. We agreed that he would simply support that this cloning experiment was inadvertent and was due in part to his ineffectiveness in clarifying the rules and communicating them effectively to the scientists.

Then, in the hearing, Margaret Mead entered with her entourage. She had a large staff, like a shepherd used in days of old, and Adlai Stevenson introduced her with the most fantastic adulatory comments. Then she lambasted us and our motives and pointed out the dangers inherent in the work. Afterwards, the NIH group was called to testify and Stevenson in particular reprimanded Fredrickson, and our agreement dissolved; Fredrickson said nothing at all in support of our behavior--the fact that there was inadequate communication.

Hughes: How were you feeling as you sat through this?

Rutter: Well, I was totally amazed, of course. I was amazed at the vigor with which Fredrickson was attacked, and I was also amazed at how he just capitulated and did not candidly discuss the situations which existed.

Afterwards, I sent a letter to Stevenson and Schmitt. I have letters from both of them.¹ Their position was that there was no excuse [for using an uncertified plasmid]. Schmitt particularly emphasized this. He had participated in the atom bomb work and was familiar with security and experimentation with hazardous materials. Of course, we weren't familiar with hazardous materials and security like that.

¹ Harrison Schmitt to Rutter, January 10, 1978. (Rutter correspondence, MSS 94-54, carton 2, folder 24.)

The Synthetic DNA Approach

Rutter: During that period, we carried on serious discussions with Bob Swanson and Herb Boyer, as well as Keiichi Itakura and Arthur Riggs, who were at City of Hope but were affiliated with Genentech. The discussions centered on one, how best to synthesize human insulin, and, two, what was the role of the university in all of this. Itakura proposed to convert rat insulin to human insulin via partially synthetic means. This was an attractive technological program, emphasizing his chemical strengths. The experiments were fascinating and would have been a beautiful way to exemplify a combination of chemistry and biological cloning. I was really positive about those experiments myself. I thought that the initial conversations Howard had had with Itakura were very good ones, and I was for those without any doubt.

The Cloning Approach

Rutter: The second major issue was cloning the human insulin gene (cDNA). The conversion of rat to human [insulin] was interesting and I was for it but that was largely somebody else's work. During this interval, Howard was trying like crazy, and so were the rest of us, to attract somebody to UCSF who could do the chemical synthesis, in case the collaboration with Keiichi Itakura didn't work out. I was committed to finding a salary for a nucleotide synthetic chemist at UCSF who could do this kind of work.

Hughes: Were there very many?

Rutter: Not too many, but there were two or three people. There were two or three major labs engaged in nucleic acid chemistry--Lord [Alexander] Todd in England, and Gobind Khorana. Gobind and his students were the most appropriate for a project of this kind.

Hughes: Was there a reason why those people didn't come to UCSF?

Rutter: It was purely a matter of persuading them. Many had other research interests and very good jobs elsewhere. Putting together the resources was difficult, and Keiichi Itakura had more experience. Itakura was a consultant of Genentech, so Genentech had some rights but didn't have a call on all of his activities. So we were talking about an independent collaboration.

Competing Cloners

Rutter: Then came the issue, who is going to do the cloning for the human insulin cDNA? On this subject, of course, there were a lot of different opinions. Herb Boyer wanted to get involved to be sure. Genentech--Bob Swanson--wanted to do it. Howard wanted to do it, and we wanted to do it. I was perfectly willing for a collaboration, but one must involve UCSF scientists.

Hughes: Wally Gilbert was somewhere out there, too.

Rutter: Well, of course, he was obviously a major competitor. I was just talking about our local group. Everyone in the field was interested. Don Steiner was crazy trying to clone human insulin. Everyone who was able and interested was trying to do this. I wasn't willing to give up the cloning project; no way was that going to happen. I was perfectly willing to have a relationship in which the value of the insulin gene would be transmitted to somebody else--to some other group that would be able to develop it commercially if it had a commercial future. But there was no way we were going to give up on the science.

I think that the same was true for Howard. He wanted it for himself and he was not going to give it up to somebody else. Because Herb had not included Howard in Genentech--Howard believed that he should have been included as an author in the original [1973] Boyer-Cohen publication--he was even more concerned about who was going to get the acclaim for cloning human insulin.

This was a difficult time; it was impossible to have an easygoing collaboration because of the personalities involved. Both groups essentially went forward on this more or less competitively. We anticipated a program with Genentech, with us doing the biology and molecular biology, and Genentech doing some of the rat/human conversion.

Movement Towards Commercialization

Commercial Interest in Insulin and Growth Hormone

Rutter: Meantime, during that summer [1977], after publication on the insulin cloning experiments, there was great interest by companies. Every company involved in insulin manufacture came to

see us. They wanted the clones. To some extent this was very surprising to me because it wasn't clear to me that there was a tremendous commercial value in the insulin gene expression. I wondered whether it would be used just because it was "human" insulin. Beef or pork insulin had worked well for decades. Pork insulin seems about as good as human insulin; beef insulin sometimes produces antibodies. This leads to requirements for higher doses, which sometimes can be a problem.

Hughes: Doesn't that very fact imply that there was a commercial value to human insulin?

Rutter: Yes, of course, there was an argument. However, if you just change one process to the other, then it is a question of how much additional value you have created.

That is not the same situation with growth hormone. Growth hormone was only available from human cadavers. One couldn't use animal growth hormones, since they were quite immunogenic and also apparently did not interact with the growth hormone receptor. Further, there the presumed need was greater than the supply. There was no great need by diabetics for another kind of insulin because diabetics were by and large being served quite well by the animal insulins, and, as far as I know, even today it is extremely rare, if ever, that a diabetic cannot be treated by animal insulins, especially pork insulin.

Hughes: Then why was there commercial interest?

Rutter: Well, in the end, I learned there was intense interest in the technology as a process which could be scaled to any demand. It was difficult to meet projected demands for insulin from demographic models. Further, it was costly to isolate the insulin from these animal pancreases, but it wasn't a situation where human insulin was absolutely required, at least to my knowledge. The technology was relevant to many other gene products, but not for insulin per se.

In this context, after the rat gene cloning, I tried to gain some perspective on the commercial value when I called Roy Vagelos. He had just left his position as head of the Department of Biochemistry at Washington University in St. Louis to become head of Merck, Sharpe, and Dohme. Merck didn't make insulin, but of course this was an issue for Eli Lilly and for other companies selling insulin--Novo, Hoechst, Nordisk.

Probably the big question at that time, and I wasn't wise enough to realize this at the time, was whether another group might enter the profitable insulin market with a product more

attractive to patients and doctors alike. The old insulin manufacturers had networks for isolating pancreases, so it was very difficult for another party to get into the market because they would have no commercial source of pancreases. My hunch is that the most active concern of these companies was that somebody else would enter a profitable market. So in the fall of 1977, we considered the possible outcome of this work.

The Hepatitis B Vaccine Project: Demonstrating the Value of the New Technology

Rutter: After the congressional hearings, and the Wade article, I became very much interested in the issue of benefit versus risk of biotechnology, how to best develop a system that would feature the value of this technology. And that led to the hepatitis B program. It led also to programs for the more effective expression of gene products in heterologous systems, and it led to my interest in technology transfer.

Proposing a Nonprofit Corporation to Commercialize Biotechnology Products

Rutter: Contemporaneously, I had a number of meetings with a group of attorneys in San Francisco--the senior attorney was Raymond Hanson--on setting up a nonprofit corporation which would benefit from commercialization of biotechnology products from UCSF. I had gone to the dean, Julius Krevans, and the chancellor, Philip Lee, with the notion that we should really set up a technology transfer lab. I was persuaded at the time that this was a good way to ensure that the discoveries and development that occurred in the university would reach the marketplace as soon as possible.

Hughes: How did you actually envision that happening?

Rutter: The idea was that the nonprofit corporation would be essentially an arm of the university. It would receive funds from a corporation that had an interest in the product derived from UCSF discoveries. The nonprofit corporation would use funds from a corporation and/or the university, however that worked out, and would receive royalties which it would split with the university and would be used internally to self fund and continue to develop a scientific enterprise. That idea was in conflict with the UC

patent office which wanted to keep all royalties. Of course, they weren't getting any royalties at the time, and they weren't negotiating for top royalties.

The UC operation was run by Josephine Opalka. I think Jo was an enterprising executive associate, but not a professional. The record speaks for itself.

I have seen a letter from Jo Opalka which refers to my attempts to get royalties for the nonprofit corporation. Nowhere had it been contemplated that I would receive royalties. On the other hand, as an inventor, I was entitled to share in the royalties enjoyed by the university.

In contrast to the university's traditional interests, clearly, I was trying to shift the university's policy to both incenting and rewarding individual research organizations for their own research activities. I did not favor our royalties going to Berkeley.¹ We wanted to keep them here on our campus. That was a major fight.

Secondly, this proposal was complex. For example, how would the institute deal with Bob Swanson and Genentech? We wanted a high royalty rate, somewhere between 5 and 8 percent, which would then be split somehow with the university according to guidelines which had not yet been established. We wanted to split royalties with the university. We said we would have labs in the UC facility, so it would be a contract with the UC Board of Regents.

All of this was very explicitly developed with the help of Raymond Hanson. Then we talked about it with various patent attorneys. There were quite a few people involved.

At the time of the congressional hearings, I was asked if the cloning had a commercial motive. I said no. The fact that Howard and two colleagues had had discussions with Genentech, and the fact that I was supposed to have met with the Genentech group on April 21 [1977] or thereabouts was given as evidence that there was a commercial motive. But this was after the fact. There absolutely was no deal that was struck during these time intervals.

In the end, we didn't make a deal with Genentech.² Instead, we had gone very far to set up a nonprofit corporation. This fact, I think, illustrated what our motives actually were during this time frame, but more than that, I honestly believed there

¹At that time, the UC patent office was located on the Berkeley campus.

² For Swanson's view, see his oral history in The Bancroft Library Series.

was no commercial motive at the time. I had never had a single conversation with anybody at UCSF along the lines that we had better do this because there was a lot of money in it, or we had better make a decision on the basis of a monetary outcome. It absolutely was scientific competition driving us.

There is also no question in my mind that Howard wanted scientific acclaim rather than money. If he had really wanted to operate for money alone, he could have done that collaboration with Genentech. No question at all about it. In fact, I know he wanted the acclaim all by himself; he didn't want me in it; he didn't want anybody else in it; he wanted that all by himself. I had similar motivations in part. I didn't care if I was involved as a partner, in fact I preferred it, but there was no way I was going to be excluded from these experiments once I got started with them. For sure it was not going to be another program out of Genentech. I was more concerned about it being an activity that came from my lab and this department at UCSF. I was very protective about that. I was adamant.

So Bob Swanson kept negotiating on rights, organization, and royalties. We learned later during that same time frame he had set up an independent plan to clone the human insulin gene with a Japanese named Okomoto who had been a friend of Keiichi Itakura's. Genentech contracted with Okomoto to provide messenger RNA to Herb Boyer who would make the cDNA and try and get the insulin cDNA clone independent of us. At the same time, Bob Swanson was introducing us to Tom Perkins and the rest of the people of Kleiner & Perkins who were the major venture capitalists supporting Genentech. Thus Boyer was also carrying out this foray to try to clone the human insulin gene independently of us. He probably figured that he would do it differently. In the end, Swanson might have thought that the cost was too high.

By the way, the nonprofit institute contemplated that the inventors could have consultant relationships for whatever they were worth and also could get shares, but the royalties themselves came to the university. I thought that was a good way to reward all the people associated with us. After initial discussions, the negotiations continued to lead nowhere, but kept us from talking to other groups. I went to the university to ask if they had any resources that we could use to develop this program. We didn't have adequate revenues from NIH to carry on the experiments. There was a lot of competition, so we felt we had to do something quickly. The university didn't have any "available" resources. They were very happy to set up the nonprofit institute if we had the money.

Hughes: Was that really all there was to it?

Rutter: That's all there was to it.

Hughes: Money, or lack of it, was really the only issue?

Rutter: There could have been other issues that were discussed at the university, like the one that was brought up by this letter from Opalka implying that there was some kind of subterranean motive on my part.

Hughes: But nothing along the lines that the university shouldn't encourage commercialization?

Rutter: There were discussions by some members of the faculty that the university should never get involved in this kind of activity. But the leadership of the university, particularly our [UCSF] administration, was quite attuned and supported this concept. I know Julie Krevans and Philip Lee were for it and had been from the beginning. Both have become more aggressively involved in later years. However, it is my hunch in the end that they didn't want it to happen. If they did want it to happen, the dean and the chancellor had enough funds to make it happen. I think it was too controversial. I don't think our administration was known for being very decisive on these matters.

I believe their position may have been wise in hindsight. There were fundamental problems about the university getting involved. If they had done it well, it would have served them well, but the chances of doing it well were not so high. If they had acted decisively in those early days, a lot of the fundamental technology would have been associated with this campus; I have no doubt about that. If Gordon had been alive, he might have just been able to swing opinion. But with me basically being alone on this, it was impossible. At any rate, that is the way it happened.

The UCSF-Lilly Agreement Regarding Insulin and Growth Hormone

Rutter: We wanted any agreement to be with an American company.

Hughes: Why was that important?

Rutter: Well, it was important because the research was to enlarge a measure of the Federal Government supported by NIH. We were after

all an American university. If there was any gain to be obtained, our first reaction would have been to do it with an American company, absolutely.

We eventually made an agreement with Eli Lilly, in particular with Irving Johnson and Paul Burnett. Johnson was head of research, biological research I guess, and Paul Burnett worked for Irv as a section chief. Eventually it turned out to be genetic engineering. He didn't have much experience in that field, but the contract called for significant royalties, 3 to 5 percent, much higher than Genentech ever paid the university.

Hughes: Was that something you negotiated?

Rutter: Yes. Everybody has recounted the fact that I always argued for high royalties; but I didn't consider those to be high royalties for the value. But it was being presented as an overbearing royalty. On the other hand, I had been led to believe from others who had more experience than I had that these were reasonable royalties. I had obtained those numbers in part by talking to people like Roy Vagelos.

The UCSF Growth Hormone Project

Rutter: While all this was happening, there was a parallel program proceeding with growth hormone. The growth hormone program was not mine, of course, but in principle I thought it was more interesting from a commercial point of view, for the reason I mentioned before, that growth hormone was a product that was really needed. At the time, nobody saw it as anything beyond treating hormone-deficient children. Nobody saw it as making bigger athletes and so on, but everybody recognized that human cadavers were limited sources.

Of course, the original work on the structure and function of growth hormone had occurred on the UCSF campus, so it was a totally appropriate development for this campus. Peter Seeburg and Howard Goodman focused on growth hormone, with John Baxter. John Baxter came from Gordon Tomkin's lab. Gordon had gotten John his job at UCSF, but they became distant in the last year or two. Gordon didn't respect John's research tactics as a scientist, in part because when John began setting up his lab he began extending the work he had done in Gordon's lab. Gordon believed that was absolutely the wrong thing to do, so Gordon was trying to get me to fire John or in some way get rid of him.

On the other hand, the people in Medicine really liked John. John was very active and entrepreneurial and extremely aggressive in setting up problems, but not so effective in carrying them out. So it wasn't any surprise that at the same time that the pBR322 experiments were being carried out, he was trying to get into the genetic engineering game. Early in January [1977] he was making a grant application for cloning growth hormone in collaboration with Peter Seeburg of Howard Goodman's lab. John is fun to be around and a person who has a great deal of ability to sway a conversation by virtue of his charm, and so I think one of the things he did very early was to get close to Peter Seeburg and John Shine. They became good collaborators of John Baxter.

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Rutter: This situation made Howard angry, because ordinarily collaborations were negotiated between professors, and groups in other professors' laboratories were more or less off-limits. There was an unwritten law that you didn't use another person's research personnel to foster your own program. John at least came very close to doing that in the case of Peter Seeburg and John Shine.

Howard Goodman and His Laboratory

Rutter: It is my view that these actions tended to make John and Peter and to some extent Axel somewhat estranged from Howard. Axel was closely related to Seeburg. They are both Germans and graduated from Heidelberg. They were more or less independent agents. This was tremendously worrying to Howard because Howard was control oriented. But Howard also liked to work in the laboratory himself. He allowed people the freedom of designing their own project.

Howard operated more on the European tradition than we did. We hired Howard from the University of Geneva where he worked in a relatively famous molecular genetics lab, headed by Tissieres. It was an international lab and very well recognized. There were several Americans there. Epstein was extremely well known at the time, and he recommended Howard to us. Howard was particularly expert in DNA biology and chemistry and in dealing with microbial systems. His background was absolutely great for this work, and he was exactly what we needed.

Howard was a person who paid attention to setting up technology. He was an excellent scientist, but as a

technologist, as an individual who was interested in the details of a technology, Howard was superb. He was ideal for setting up sequencing, setting up ways to purify DNA and RNA, setting up means to improve vectors, setting up computers to organize data collection, and all of the related technologies which were absolutely required for cloning. Howard spent most of his time doing that.

He was absolutely critical to the technological underpinning of the department. None of the individuals who actually participated in the cloning would have been anywhere without that help. It goes for Herb Boyer; it goes for any of the guys in his lab; and it goes for me and my lab as well. Every one of the individuals were good scientists and they added to this fundamental technological base, but it was the technological base which was being developed in this period of time in which Howard was a very key contributor. That helped everybody out. So the allegations that are mentioned in the Hall book¹ that he didn't have anything to do with X, Y, or Z are just absolutely false. Howard was interested in the detail of every experiment.

In fact that was to some extent his limitation. He wasn't as conceptually focused as he was technologically focused. His laboratory was set up as a technology lab. We needed it. In a department like ours, everybody was going to use this technology. He served the department exceptionally well and his coworkers exceptionally well. In a sense it was also true that his relationship with Baxter was good for both of them. Baxter couldn't have gone anywhere without Howard's help. On the other hand, Howard really could use Baxter's knowledge of physiology and endocrinology to become involved in a meaningful scientific study on growth hormone.

Hughes: Collaborative research was what all along you sought to have happen in the department.

Rutter: Well, yes, you know it really was. We realized that the interdisciplinary cooperativity could produce a tremendously powerful research program. Every one of the scientists that I knew had strengths and weaknesses, strong strengths and weaknesses. Wherever there was open and meaningful coordination, you found a much stronger program; I am still convinced about that. It is one of the things that was right in its conception, and it certainly is a major reason why UCSF is famous today; there is no question about it. I think it is the main reason

¹ Stephen Hall. Invisible Frontiers: The Race to Synthesize a Human Gene. Redmond, WA: Tempus Books, 1987.

that this place has flourished as compared to more distinguished universities where isolationism is the rule.

More on the UCSF-Lilly Agreement

Rutter: Back to Lilly. This program with Eli Lilly invoked a coordinated cloning for both growth hormone and insulin. I was responsible for the program, and there were three independent projects in the labs of the principle investigators. Insulin and growth hormone were the initial targets, but it was anticipated that others would come after that. The initial contract, as I told you, anticipated royalty payments, but it did not anticipate a nonprofit organization. We just couldn't swing it; it was too complicated. Lilly wouldn't have anything to do with it; the university was not as interested as I hoped, and it became obvious, it was quite complicated.

In those initial agreements, there was a royalty for patentable material and very much less for nonpatentable technology; there was a tremendous discrepancy between them. We didn't know at that time that Lilly was at the same time collaborating with Genentech. Later on, we found out, but it was probably just before Genentech announced that it had cloned the synthetic cDNAs for the B- and the A-chains of insulin, the synthesis derived from Keiichi Itakura. They then employed a process developed in Berkeley by a professor named Fred Carpenter and his students for combining the two chains to insulin.

Consultantships and Patent Positions

Rutter: As part of the program with Eli Lilly, we were given consultantships. I think it was ten or twelve thousand dollars a year for each of the senior investigators and a few thousand--I'm not sure what it was--for each of the postdoctoral fellows. This arrangement was exceptional in itself. No one in the laboratory had gotten any money from these kinds of contracts in other instances, to my knowledge.

Hughes: And that was something you arranged?

Rutter: Yes. There were two people involved in my laboratory, Raymond Pictet and Graeme Bell; three people in Howard's lab, Axel Ullrich, John Shine, and Peter Seeberg; and one person in John's

lab, Joseph Martial. I think there were twenty-six additional people involved in the research.

Then the university began developing a patent position through its patent office. Of course, we didn't know anything about it. But because of the early contact with Lorrie Greenlee and his previous career in biology, we encouraged him to be the patent attorney. But we also had talked with Bert [Bertram] Rowland, who had written the Boyer contract¹ and was a patent attorney for Syntex and for Syva.

The programs then developed as we openly interacted with Eli Lilly. We developed strategies and applied for patent applications which came from these strategies. One was derived from a patent application that I wrote by myself. However, it never issued because of a competing patent application from Genentech. That method was used in the growth hormone synthesis by Eli Lilly.

Lorrie Greenlee developed a patent application for the general methodologies of expression in the name of the principle investigators, Howard, John Baxter, and myself. That application caused a big problem with all of the guys in the laboratories because the application involved examples from our laboratories. The researchers who were developing examples thought that they should be inventors. This was different than the insulin case, for example, because all of the people who were associated with the project were included as inventors, more or less as in a scientific paper.

But the patent application was a conceptual patent on expression in general, not on a particular solution. This issue was dealt with by allowing the patent attorney to make the determinations. If any money came from these patents, we would share it with all those who contributed significantly, independent of the patent inventorship.

Hughes: That's possible when the names aren't on the patent?

Rutter: Yes. On every single one of the patents that I hold, I share royalties with everybody. Everyone gets a share of the patents but they don't get equal shares. Even technicians get royalties.

Hughes: Was that common at that time?

Rutter: No, absolutely not. I still don't think it's common. I think it was most common for the professor to keep patent royalties and to think everything associated with the program was fungible. That

¹Rowland was the patent attorney for the Boyer/Cohen recombinant DNA patents.

is, they were students who were associated with the program more or less by accident.

In our case, Eli Lilly was getting a lot of technology. They were developing their own programs that were based on our methods. They were trying to clone hamster insulin cDNA, for example. They were going to use this as a way to go to human insulin.

Ullrich and Seeburg Join Genentech

Rutter: Howard Goodman's laboratory and my own cooperated (with a few rough spots). Axel became very assertive about what he was and wasn't going to do, and Peter Seeburg was really in control of the growth hormone project. Howard was still on sabbatical for part of 1976 and all of 1977. We heard that [Axel and Peter] were having discussions with Genentech and also with Cetus. So Howard, John, and I went over to talk with executives at Cetus. One of the people from Gordon Tomkin's lab, David Gelfand, who had been in my lab for a period after Gordon's death, had taken a job at Cetus as director of research. It was clear that Peter and John and Axel had been negotiating. All of the sudden these guys went to Genentech and took the clones with them.

So there was a major problem, aside from UCSF ownership of the clones, because we had a contract with Eli Lilly. In the end, this is what Genentech wanted all along! It got for much less stock and for much less money up front, and for virtually no royalties from the university, the technology transferred! To this day, I don't know exactly how it happened.

Axel, and especially Peter, had a poor relationship with Howard. Axel would alternately play Howard against me and then me against Howard: With me, Howard was the problem, with Howard, I was the problem. In part, I could understand. He had a right to be worried; I was not going to allow Axel to be the sole "cloner." I set up a competing program with Graeme Bell, a graduate student who was an excellent technical person. Howard had set up a program in his lab with Barbara Cordell and a few other people.

Hughes: Were these competing programs one of the reasons that Axel and Seeburg left UCSF?

Rutter: Seeburg had his own reasons for leaving because he was more or less in control of the growth hormone project. But there were

others on the project, so it could have been that he wanted to leave for that purpose. In Axel's case, for sure, he wasn't going to be the only cloner. So that might have been part of the reason why he left. But there was also the issue of whether they were going to get adequate rewards for their work, and I think the pBR322 cloning incident was a major issue. Their future in the academic world might not be secure. At that time, commercial organizations were not subject to the guidelines.

As a result of the constraining environment [at UCSF], perhaps they believed they weren't being treated with the respect that they deserved, so there was a number of different reasons for them to leave. I think it was a combination of the opportunity, as exemplified by salary and stock options, and the chance for an independent career.

The net result of the negotiation was a concern about who owned the technology. The university had awarded Eli Lilly exclusive rights to the commercial outcome of the insulin and growth hormone deals. Axel and Peter had also been paid by Eli Lilly before they went to Genentech. What to do? Howard felt that he couldn't prohibit the transfer despite the fact that it was a commercial organization. I honestly don't know why he took that position. We asked for the [UC] legal and patent offices to get involved and counsel us. What was right in a circumstance like this?

A Conspiracy between Genentech and Lilly?

Rutter: I got concerned because I was in charge of the contract with Eli Lilly, and therefore I believed that these folks had rights to all of this material. The negotiation was made primarily by the patent office and the patent attorneys. I wrote to Roger Ditzel, who was then head of the [UC] patent office, saying we should get together before the negotiation and bring in the people from Eli Lilly to help the university make a decision. We did have such a meeting. The people from Eli Lilly did not take a position, which also totally surprised me.

Hughes: Why was that?

Rutter: I don't know, but in the end, the settlement that the university made with Genentech was extremely disadvantageous [to the university]. Of course, they believed they gave the material for investigational use only, and this deal did not preclude royalties for commercial use.

Hughes: Do you attribute that to UCSF's ineptitude alone?

Rutter: I personally believe that there was a conspiracy between Genentech and Eli Lilly, such that there would be one royalty rate paid by Genentech to Eli Lilly, and the university would get none, and by this skinny settlement, Lilly absolved itself of any responsibility to go further with the program. Eli Lilly subsequently gave approval for Howard Goodman to become a consultant of Hoechst. I also thought this was incredible because after all he was a major consultant for Lilly.

It all fits into place if you assume that a plan existed at that time. Eli Lilly was going to pay no royalty to the university, claiming that there was no technology in the transfer. Interestingly, Walter Bunting, the attorney who set up the relationship with the university, went to Genentech. The partnership which we had tried to set up with Eli Lilly never really materialized. In hindsight, it made sense that they didn't pay attention to our intellectual property. They didn't want the applications to be strong enough to protect, because then they would have to have paid royalties. They got everything that we had during this time frame, and we got nothing from them. In hindsight, these legal battles and the current patent suit makes sense in this context.¹

¹ "The current patent suit," for which Rutter and other scientists mentioned in the oral history made depositions, involved Eli Lilly, the University of California, and Genentech. For details of this complex legal battle, involving suits and countersuits and in which the pBR322 episode figures prominently, see Nature Biotechnology 1997, 15:307 (April). Also see the appendix for an update in the March 6, 1998 issue of Science.

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CURRICULUM VITAE

WILLIAM J. RUTTER

Birthdate: August 28, 1928
 Birthplace: Malad City, Idaho

EDUCATION

1946-1949	B.A.	Harvard University	Biochemistry
1949-1950	M.S.	University of Utah	
1950-1952	Ph.D.	University of Illinois	Biochemistry

AWARDS AND HONORS

1967	Pfizer Award in Enzyme Chemistry, American Chemical Society
1981-2	Faculty Research Award, UCSF
1983	J.J. Berzelius Award, Karolinska Institutet, Stockholm
1984	Member, National Academy of Sciences
1986	20th Brown-Hazen Award and Lecturer, State of New York Department of Public Health
1986	Kroc Visiting Professor, Joslin Diabetes Center, Harvard University Cambridge, MA and University of Texas Health Science Center, Dallas
1987	Member, American Academy of Arts and Sciences
1987	Bertner Award, M.D. Anderson Hospital & Tumor Institute, Houston, TX
1993	Member, Fellowship of the International Institute of Biotechnology
1993	Fellow, American Academy of Microbiology
1992-96	Member, Harvard Board of Overseers
1995	Heinz Award for Technology and the Economy
1996	Honorary Doctorate, University of Illinois
1996	Honorary Professorship of Science, Eotvos University, Budapest
1996	Honorary Doctorate of Science, Eotvos University, Budapest
1996	University of California, San Francisco Medal

PROFESSIONAL POSITIONS

1952-1954	USPHS Postdoctoral Fellow, University of Wisconsin Institute of Enzyme Research, Madison, Wisconsin
1954-1955	USPHS Postdoctoral Fellow, Biochemistry Department Nobel Institute, Stockholm, Sweden
1955-1960	Assistant Professor, Division of Biochemistry, Department of Chemistry, University of Illinois, Urbana, Illinois
1960-1963	Associate Professor, Division of Biochemistry, Department of Chemistry, University of Illinois, Urbana, Illinois
1962-1963	Visiting Scientist, John Simon Guggenheim Memorial Fellowship, Stanford University

1963-1965	Professor, Division of Biochemistry, Department of Chemistry, University of Illinois, Urbana
1965-1968	Professor, Departments of Biochemistry & Genetics, University of Washington, Seattle
1968-1982	Chairman, Department of Biochemistry & Biophysics, University of California, San Francisco
1968-Date	Hertzstein Professor of Biochemistry, Department of Biochemistry & Biophysics, UCSF
1981-Date	Chairman of the Board, Chiron Corporation, Emeryville, CA
1983-1989	Director, Hormone Research Institute, UCSF

EXTRAMURAL APPOINTMENTS

National Institutes of Health

Physiological Chemistry Study Section	1967-1971
Member, Board of Scientific Counselors, National Institute of Environmental Health Sciences	1976-1981
Various ad hoc boards and study sections	To date

National Science Foundation

Developmental Biology Panel	1971-1973
National Science Board Special Commission on the Future of the National Science Foundation	1992

National Academy of Sciences

National Research Council	1969-1972
Member, Executive Committee, Division of Biology and Agriculture	

<i>Food and Drug Administration Science Advisory Bd</i>	1993-1999
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National Laboratories

Los Alamos Scientific Laboratory, Biomedical Advisory Committee	1972-1975
Advisory Committee on Biosciences & Biotechnology	1993-
Oak Ridge National Laboratory	
Biology Division Advisory Committee	1976-1980
Advisory Board of ORNL & Martin Marietta Energy Systems	1984-1987
Naval Biosciences Laboratory, Oakland, Ca	1982-1984
Member, Scientific Advisory Committee	
Advisor, Joint Livermore-Los Alamos National Laboratory Project to construct a chromosome-specific human DNA library	1983-1987
Scientific Review Committee, Scripps Clinic and Research Foundation, La Jolla, CA	1979-1982
Scientific Advisory Committee, Scripps Clinic and Research Foundation	1986-1988
UCLA Symposia on Molecular and Cellular Biology Advisory Board	1985-1988

International Laboratories

Hagedorn Research Laboratory, Nordisk Laboratorium, Copenhagen, Member, Scientific Advisory Board	1980-1986
German Center for Molecular Biology of the University of Heidelberg, Member, Scientific Advisory Board	1983-1987
International Centre for Genetic Engineering and Biotechnology, Member, Panel of Scientific Advisors	1984-

Foundations

National Cystic Fibrosis Research Foundation	
Member, Basic Science Advisory Committee	1969-1974
Chair, Basic Science Advisory Committee	1972-1974
President's Advisory Council	1974-1975
March of Dimes Basic Research Advisory Committee	1976-1987
Keystone Life Science Study Center	1983-
Board of Directors	
California Council on Science and Technology	1990-
Life Sciences Research Foundation	
Member, Advisory Board of Trustees	1989-

Societies (Offices Held)

American Society of Biological Chemists	
Treasurer	1970-1976
Representative, Council of American	
Association of Medical Colleges	1973-1976
Pacific Slope Biochemical Conference, President	1975-1976
American Society for Developmental Biology,	
President	1975-1976

Editorial Boards

Archives of Biochemistry and Biophysics	1978-1985
Developmental Genetics	1980-1983
Diabetes	1982-1985
DNA	1980-1983
Journal of Biological Chemistry	1976-1979
Journal of Cell Biology	1976-1979
Journal of Experimental Zoology	1968-1971
Molecular Biology and Medicine	1982-
PAABS Revista, Advisory Board	1971-1977
Molecular Endocrinology	1986-1991
Protein Engineering	1986-1991

Consultantships

Abbott Laboratories, North Chicago, Illinois	1960-1975
Eli Lilly Co., Indianapolis, Indiana	1977-1980
Merck and Co., Rahway, New Jersey	1977-1981

Scientific Advisory Board

AMGEN, Newberry Park, CA	1979-1981
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Board of Directors

Hana Biologics, Berkeley, CA	1980-1983
Meridian Instruments, Ann Arbor, MI	1982-1988
Chiron Corporation, Emeryville, CA	
Chairman of the Board	1981-
Harvard University Board of Overseers	1992-1999
Ciby-Geigy Board of Directors	1995-

Carnegie Institution of Washington
Board of Trustees

1995-

PUBLICATIONS

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2. Hansen, R.G. & Rutter, W.J. (1952). Fatty acid metabolism of rat diaphragm. *J. Biol. Chem.* **195**, 121-6.
3. Hansen, R.G., Rutter, W.J. & Craine, E.M. (1952). A nephelometric method for the determination of glycogen. *J. Biol. Chem.* **195**, 127-132.
4. Rutter, W.J. & Hansen, R.G. (1953). Lactose metabolism. I. Carbohydrate metabolism of *Lactobacillus bulgaricus* strain gere A. *J. Biol. Chem.* **202**, 311-321.
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17. Rutter, W.J. (1960). Some aspects of the regulation of growth in cell systems. In: *Biochemistry of morphogenesis*, Fourth Internatl Congr. of Biochemistry, Pergamon Press, New York, pp. 20-29.
18. Brosemer, R.W. & Rutter, W.J. (1961). The effect of oxygen tension on the growth and metabolism of a mammalian cell. *Exptl Cell Res.* **25**, 101-113.
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BIOGRAPHICAL INFORMATION

May 1, 1984

WILLIAM J. RUTTER, PhD

Pioneering molecular biologist William J. Rutter, PhD, is Hertzstein Professor of Biochemistry at the University of California, San Francisco, and director of UCSF's Hormone Research Institute.

Rutter is well known in the area of recombinant DNA technology, having achieved the first major triumph of genetic engineering in 1977 when he, UCSF colleague biochemist Howard Goodman and their research teams successfully isolated the gene for the hormone insulin from rats, and transplanted the gene to bacteria.

The experiment was the first step toward genetically engineering microorganisms to produce hormones and other biomedically useful substances. Today, bacteria as well as yeast are routinely employed as "factories" to produce insulin and many other biological substances.

Rutter's main interest has been in the structure of genes and the mechanism by which genes are expressed -- that is, how they are turned on or off, or their activity modified. He first studied the catalysts in humans and other animals involved in expression of the genes, and then turned his attention to the genes themselves. Besides insulin, he has contributed significantly to present knowledge of the structure of genes for other peptide hormones, including epidermal growth factor, a hormone that regulates the growth of epithelial cells, nerve growth factor, a hormone that controls the growth of nerves, glucagon, a hormone controlling carbohydrate metabolism, and somatostatin, a hormone that regulates a number of other hormones.

More recently Rutter and his group have turned to the problem of the regulation of expression of the genes in specific differentiated cells. He and his colleagues recently discovered the regulatory sequences of DNA that precede the genes, and which control their activity in the particular cells in which they are expressed. Their studies hold promise for revealing the mechanism by which genes are turned on in certain cells during embryological development.

He also has been a leader among scientists in applying genetic engineering techniques to the analysis of hepatitis B virus, in hopes of producing an

(more)

mailed and messengered: 5/1/84

inexpensive vaccine against the disease. Collaborating with a group at the University of Washington, he and coworkers at UCSF and Chiron Corporation in Emeryville, California, first cloned the gene for the outer coat of the virus -- the part of the virus that stimulates the immune system to mount an attack against it -- and in 1981 inserted it into bacteria and yeast. The yeast cells subsequently assembled a pseudo-virus particle that was indistinguishable from the natural virus, except that the synthetic virus was not infectious. Chiron scientists have successfully produced the viral coat (called the surface antigen) in quantity, and the drug company Merck Sharpe & Dohme currently is conducting clinical trials of the genetically-engineered vaccine.

Rutter and colleagues at UCSF also are studying the link between the hepatitis B virus and a deadly liver cancer called primary hepatocellular carcinoma, specifically how the integration of the hepatitis virus DNA into the liver cell's DNA may affect the cell's function and the later development of cancer.

A graduate of Harvard University, Rutter received his PhD from the University of Illinois. He did postdoctoral work at the Institute for Enzyme Research at the University of Wisconsin, Madison, and at the Nobel Institute in Stockholm, and then moved to the University of Illinois's chemistry department, eventually ascending through the ranks to become full professor. He left Illinois for the University of Washington in Seattle, and remained there until coming to UCSF in 1969 as professor and chairman of the department of biochemistry and biophysics. As chairman he built the UCSF group into one of the country's foremost departments in this field. In 1982 he stepped down as chairman and in 1983 was named director of the Hormone Research Institute.

Rutter is the author of more than 200 scientific papers, and has served on the editorial boards of various scientific journals. He also has been an advisor to many national and international laboratories and scientific organizations. Of the various honors he has received, the most recent was the 1983 J. J. Berzelius Prize of the Karolinska Institutet in Stockholm.

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In photo, left to right: William Rutter, Raymond Pictet, John Chirgwin, Axel Ullrich, Ed Tischer, John Shine, Howard Goodman.

TIME

INSIDE:
Ready, Set, Sweat!

MEDICINE

One for the Gene Engineers

Of all the possible benefits promised by the controversial new work with recombinant DNA (TIME cover, April 18), none has been more widely publicized than the mass production of insulin by re-engineered bacteria. If these tiny insulin factories could indeed be created



SAN FRANCISCO TEAM & GENE
Turning bugs into factories.

in the laboratory, they would yield a virtually unlimited supply of the hormone, which is of vital importance to many diabetics. Last week scientists at the University of California in San Francisco reported that they had taken an important first step toward that goal. Using the bold new technology, they not only gave a bacterium potential insulin-making capability but also got the bug to reproduce millions of precise carbon copies of itself, all with the same new characteristic.

The work bodes well for the world's millions of diabetics. The insulin for their daily shots is for the most part extracted from cow and pig pancreases obtained from slaughterhouses. But some diabetics develop strong allergic reactions to animal insulin. Both for this reason and because of the increasing demand for the hormone, which the body needs to turn sugar into energy, drug companies seeking alternative sources have pinned some of their hopes on recombinant DNA technology. By inserting the human insulin gene into the DNA of the common intestinal bacterium *Escherichia coli*, they could, in theory, endow the bug with the capacity to make human insulin.

In the achievement announced last week, Biochemists Howard Goodman and William Rutter and their colleagues did not work with human genes. Under the safety guidelines adopted by the National Institutes of Health (to lessen the risk of accidentally producing an *E. coli* that might be harmful), such less readily available material would have required a far more stringent level of physical containment in the lab than any yet available. Instead, they experimented with insulin genes from rats. Placing this foreign DNA inside enfeebled *E. coli*, they were delighted to find that the genetic material was replicated every time the bacteria divided. But the scientists do not yet know whether the rat genes—in the language of molecular biology—actually expressed themselves, that is, produced insulin.

No matter; the experimenters are convinced that they will soon be able to "switch on" the genes. Said Rutter: "I'd be surprised if it took more than a year or two." The production of human insulin will probably take much longer. Yet meanwhile, the experiments themselves should help scientists clarify the complex chemistry of insulin and better understand diabetes—which is not a single disease, as was once thought by doctors, but a variety of metabolic disorders that may afflict as many as 10 million people in the U.S. alone.

The newest triumph of genetic engineering may also influence the actions of Congress, which is now considering legislation to regulate recombinant DNA research. Goodman undoubtedly echoed the views of many of his fellow scientists on the subject when he said, "It's a dangerously anti-intellectual precedent to make laws against an unknown harm."

UC gene researchers admit

Tues., Sept. 27, 1977 ☆ S.F. EXAMINER—Page 5

violating safety rules

By Walter Barney
Science Writer

Embarrassed University of California San Francisco researchers conceded yesterday that they broke the rules set to insure the safety of gene-splicing research.

Those experiments here led to UCSF's announcement last spring that researchers had isolated the insulin gene in rats, a feat that received worldwide publicity.

A team in the laboratory of Dr. Howard Goodman first spliced the rat gene into a circular DNA chain called a plasmid that belonged to a strain not certified safe by the National Institute of Health.

The strain was actually safer — perhaps as much as a thousand times safer — than the certified strain upon which the researchers eventually carried out the insulin experiment. The UC team essentially jumped the gun on the NIH certification process.

NIH guidelines for recombinant DNA research were drawn up in response to fears that the gene-splicing technique could result in



DR. HOWARD GOODMAN
Forbidden DNA chain used

the creation of new bacteria that might create epidemics of new diseases.

Goodman and Dr. William Rutter, whose laboratory isolated the genetic material that was introduced into the forbidden plasmid, said yesterday that the violation

came about because of honest confusion over the NIH certification process.

The plasmid strain, designated pBR322, had been approved by the NIH advisory committee on recombinant DNA, but not certified by director Donald Frederickson. The distinction between "approval" and "certification," Rutter said, was the undoing of the UCSF researchers.

The approval was granted informally by the advisory committee on the basis of data reported by telephone to a meeting in Miami. But formal approval was delayed pending the arrival of written data in the NIH headquarters.

Nevertheless, the UCSF team went ahead with the experiment, using pBR322.

Goodman was in Japan at the time, and the work went on under Dr. Axel Ullrich. When Goodman returned, in March, he attended another recombinant DNA meeting — this one in Utah — and learned that the strain still had not been certified.

"I left immediately for San

Francisco," Goodman said yesterday. "When I got here I called the staff together, told them what had happened, and ordered the experiment stopped."

At that point, the researchers had successfully introduced the gene into the plasmid, and inserted the plasmid into a weakened strain of bacteria called EK2. But they had not verified that the bacteria had reproduced the insulin gene.

At Goodman's order, the bacteria were destroyed. Only when a new plasmid strain, pMB9, was certified in April, was the experiment resumed.

Four weeks later, Rutter and Goodman called a press conference to announce the successful isolation of the insulin gene. They did not, however, say anything about the abortive experiment or the violation of guidelines.

Nor was the use of pCR322 recorded in the logbook of the restricted laboratory in which the insulin experiments were made.



Examiner Photos by Bob Bryant

DR. WILLIAM RUTTER
Experiment was successful

The news was not made public until this week, when *Science* magazine, the official publication of the American Association for the Advancement of Science, printed an article about the violation.

Ironically, pCR322 has now become the preferred plasmid for recombinant DNA experiments because it is much safer than any of the others.

The strain is so safe, one NIH committee member said yesterday, that it may permit relaxation of the guidelines.

The UCSF team, the member said, "was utterly within the spirit of the guidelines; they were using the safest thing around. But what they did was wrong — they've been caught with their hand in the till."

Dr. Herbert Boyer, in whose laboratory pCR322 was developed, agrees. "It was an error in judgment on the part of the people involved," Boyer said. "But they didn't jeopardize anybody."

NIH director Frederickson is out of the country. His assistant, Dr. Daphne Kamely, said that the NIH is in contact with the UCSF biohazards committee, but that any action would have to await Frederickson's return.

Dr. Rutter's achievements as Chairman stemmed from his ability to recognize and nurture good science in the work of his colleagues. This ability also guided his own research efforts. In early fundamental studies he was the first to characterize in molecular terms the development of both the endocrine and the exocrine pancreas. In this work he was the first to clone and sequence the insulin gene, and one of the first to define control regions regulating cell specific gene expression. The race to clone the insulin gene epitomized an important and dynamic period in the rise of *The New Biology*, which was described in a book, *Invisible Frontiers*. Dr. Rutter also pioneered the cloning and sequencing of other crucial proteins such as the receptors for insulin and the insulin-like growth factors. Yet his research was not confined to hormones and their receptors. His group cloned and sequenced the hepatitis B surface antigen gene, which allowed a recombinant vaccine for hepatitis B virus to be developed. In the field of protein engineering, Dr. Rutter was one of the first to apply site-directed mutagenesis to address protein/structure relationships in enzymes. Today we honor Dr. Rutter with presentations by eminent scientists who will present research in five of the areas in which he has made seminal contributions: developmental biology, gene engineering, gene control, protein structure and viruses.

Dr. Rutter's abilities have been recognized in many ways. He has received prizes for his research including the Pfizer Award from the American Chemical Society and the Berzelius Award from the Karolinska Institute. He is a member of the American Academy of Arts and Sciences, the National Academy of Sciences, the American Academy of Microbiology and the Harvard Board of Overseers. He has been a member of advisory boards of institutions both in the United States and abroad. He has been active on research foundations including the National Cystic Fibrosis Foundation, March of Dimes, and the California Council on Science and Technology. He has held office in the American Society of Biological Chemistry and the American Society of Developmental Biology. He has played a major role in bringing biotechnology to the Bay Area and is currently Chairman of the Board of Chiron Corporation in Emeryville. He remains active as a Professor at UCSF and maintains an productive research program in the Hormone Research Institute. He has also been a major contributor to the California Foundation for Molecular Biology, which supports research in New Biology at UCSF.

The organizing committee of this symposium wishes to recognize the generosity of Dr. Herbert Boyer and the Boyer Foundation of the Department of Biochemistry and Biophysics in supporting this symposium.

THE NEW BIOLOGY

A SYMPOSIUM IN HONOR OF WILLIAM J. RUTTER AND HIS SCIENTIFIC CONTRIBUTIONS DURING A QUARTER OF A CENTURY AT UCSF



Millberry Union
University of California
San Francisco, California
March 18-19, 1994

Friday March 18th

1:00 Reg Kelly: Introductory Remarks

DEVELOPMENT

1:10 Marc Kirschner: Regulation of the Cell Cycle

1:50 Douglas Hanahan: Developmental Biology of Cancer

2:30 Coffee

GENETIC ENGINEERING

3:00 Axel Ullrich: Definition of Signals in Cell Differentiation and Cancer

3:40 Rusty Williams: Signalling Molecules that Mediate the Actions of Growth Factors

4:20 Herb Boyer: The Beginning of Biotechnology

Saturday, March 19th**GENE CONTROL**9:30 Tom Maniatis: Virus Induction of the Human $\alpha 1$ β Gene Requires The Assembly of a Stereospecific Enhancer Complex

10:20 Coffee

10:40 Bob Roeder: Mechanisms of Eukaryotic Transcriptional Regulation

11:20 David Baltimore: The NF κ B 1 Gene is Required for Immune Responsiveness But Not Development

12:00 Lunch

PROTEIN STRUCTURE

1:30 Dan Koehlman: Protein Structure, Information Processing and Bill Rutter

2:10 Jim Spudich: Structure and Junction of Myosin: A Molecular Motor

2:50 Coffee

VIRUSES

3:20 Don Ganem: RNA Protein Interactions in Hepatitis B Virus Replication and Assembly

4:10 Harold Varmus: Getting Rous Sarcoma Virus Into Cells

William J. Rutter, Ph.D. Hertzstein Professor of Biochemistry

William J. Rutter came to UCSJ in 1968 to be Chairman of the newly constituted Department of Biochemistry and Biophysics. At that time UCSJ or the University of California Medical Center as it was generally known then, lacked a tradition of excellence in biochemistry and molecular biology. Dr. Rutter recruited Gordon Tomkins as his Vice Chair. Together they attracted an energetic and talented group of young scientists to his new department. Dr. Rutter and his young colleagues quickly capitalized on breakthroughs in DNA cloning and sequencing, and as a result UCSJ became one of the two major centers of molecular genetics in the world. Thus began the New Biology, the application of the powerful tools of molecular genetics to solve the outstanding problems of biology, with UCSJ at the forefront. Brilliant young scientists, attracted in considerable measure by the intellectual resources of the Department of Biochemistry and Biophysics, were recruited by the other basic science departments. Much of the current renown of UCSJ as a biomedical research center has derived, therefore, from Dr. Rutter's skill in building the Department of Biochemistry & Biophysics.

UC, Lilly Ask Supreme Court to Hear Insulin Case

Like groggy boxers, lawyers for the University of California (UC) and Eli Lilly & Co., an Indianapolis-based drug manufacturer, are staggering back into the ring for the last round of a 8-year-long, multimillion-dollar fight over who owns rights to exploit the human gene for insulin.

In petitions filed on 21 January and 20 February, each side has asked the Supreme Court to revisit a lower court's ruling that rejected UC's claim to be the rightful owner of a genetic discovery that is the basis for Lilly's hundreds of millions of dollars' worth of synthetic insulin sales (*Science*, 22 August 1997, p. 1028). Each side, of course, has a different reason.

UC claims that the trial in district court in 1995 was wrongly held in Lilly's hometown of Indianapolis and should have been held in California. UC argues that procedures based on the Constitution—which gives states sovereignty over certain disputes in their borders—were violated. UC wants to reargue the case at home.

Lilly, on the other hand, is happy with the results of the trial, which not only voided UC's claims but also ruled that UC scientists had engaged in "inequitable conduct." The district court found that UC scientists had used a cloning vector (pBR 322) that was temporarily off limits for safety reasons, and that they misled patent examiners about their research methods. However, an appeals court last year ruled that any misconduct was immaterial, while finding UC's patent suit invalid for other reasons.

Lilly is trying to persuade the court that the misconduct charge is relevant, claiming that legal costs (which Lilly estimated at \$20 million) should be paid by UC, as ordered by the district court. Lilly's brief asks: "Should scientists who conduct cloning experiments in knowing violation of applicable federal safety guidelines, and then misrepresent the origin of their work ... be entitled to enforce patent rights obtained from the illicit invention ...?" UC plans to file a rebuttal soon.

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