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Program in the History of the Biosciences and Biotechnology

Arthur Kornberg, M.D.

BIOCHEMISTRY AT STANFORD, BIOTECHNOLOGY AT DNAX

With an Introduction by
Joshua Lederberg

Interviews Conducted by
Sally Smith Hughes, Ph.D.
in 1997

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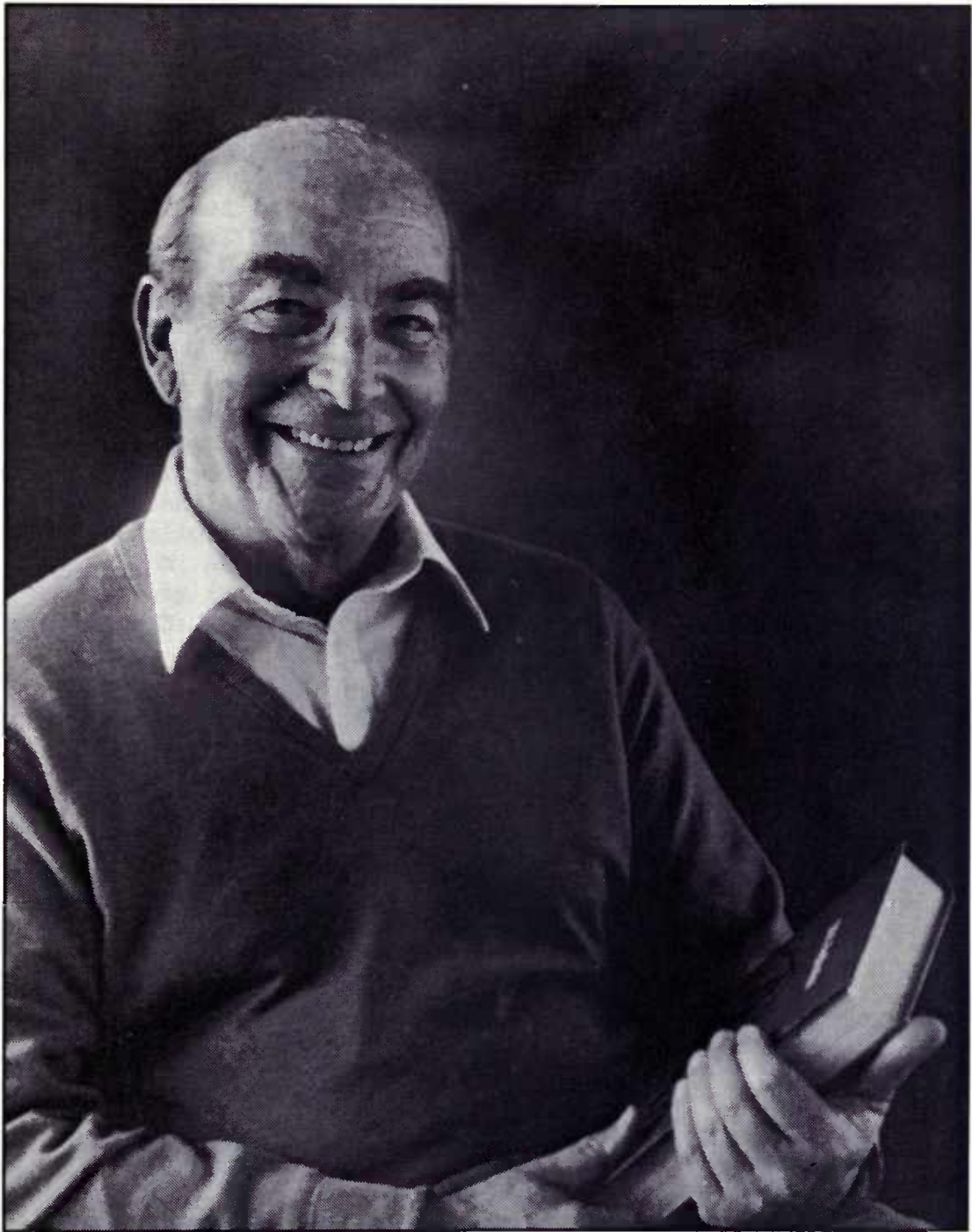
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Arthur Kornberg, ca. 1987.

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Arthur Kornberg, M.D. (b. 1918)

Biochemist

Biochemistry at Stanford and Biotechnology at DNAX, 1998, xiv, 268pp.

Early career at National Institutes of Health: nutrition research, mentored by Severo Ochoa and Carl Cori; chairman, microbiology, Washington University, St. Louis: C.B. van Niel's microbiology course, faculty, Erwin Chargaff, nucleotide chain synthesis research, DNA as genetic material; chairman, biochemistry, Stanford University: renovation of Stanford Medical School, founding and staffing of biochemistry department, interaction of basic and clinical sciences, departmental operational style, new biochemistry curriculum, industry ties, Industrial Affiliates Program; research programs: DNA polymerase, DNA replication, viral synthesis, polyphosphate, Nobel prize; recombinant DNA: Senate testimony, 1968, patenting in biotechnology, controversy, Stanford biochemistry contributions to/failure to recognize commercial potential of, Peter Lobban's research on; ALZA Corporation; DNAX: foundation, funding, and staffing, purchase by interactions with Schering-Plough, antibody and interleukin research; anti-Semitism; Paul Berg; Dale Kaiser.

Introduction by Joshua Lederberg, Ph.D., Rockefeller University, New York.

Interviewed 1997 by Sally Smith Hughes for the Program in the History of the Biosciences and Biotechnology, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

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

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

In 1996, a long-held dream of The Bancroft Library came true with the launching of its Program in the History of the Biological Sciences and Biotechnology. For years, Bancroft had wished to document the history of the biological sciences on the Berkeley campus, particularly its contributions to the development of molecular biology. Bancroft has strong holdings in the history of the physical sciences--the papers of E.O. Lawrence, Luis Alvarez, Edwin McMillan, and other campus figures in physics and chemistry, as well as a number of related oral histories. These materials support Berkeley's History of Science faculty, as well as scholars from across the country and around the world.

Although Berkeley is located next to the greatest concentration of biotechnology companies in the world, Bancroft had no coordinated program to document the industry nor its origins in academic biology. For a decade, the staff of the Regional Oral History Office had sought without success to raise funds for an oral history program to record the development of the industry in the San Francisco Bay Area. When Charles Faulhaber arrived in 1995 as Bancroft's new director, he immediately understood the importance of establishing a Bancroft program to capture and preserve the collective memory and papers of university and corporate scientists and the pioneers who created the biotechnology industry. He too saw the importance of documenting the history of a science and industry which influence virtually every field of the life sciences, generate constant public interest and controversy, and raise serious questions of public policy. Preservation of this history was obviously vital for a proper understanding of science and business in the late 20th century.

Bancroft was the ideal location to launch such an historical endeavor. It offered the combination of experienced oral history and archival personnel, and technical resources to execute a coordinated oral history and archival program. It had an established oral history series in the biological sciences, an archival division called the History of Science and Technology Program, and the expertise to develop comprehensive records management plans to safeguard the archives of individuals and businesses making significant contributions to molecular biology and biotechnology. All that was needed was funding.

In April 1996, the dream became reality. An anonymous donor provided seed money for a center at the Bancroft Library for historical research on the biological sciences and biotechnology. Thanks to this generous gift, Bancroft has begun to build an integrated collection of

research materials--primarily oral history transcripts, personal papers, and archival collections--related to the history of the biological sciences and biotechnology in university and industry settings. One of the first steps was to create a board composed of distinguished figures in academia and industry who advise on the direction of the oral history and archival components. The Program's initial concentration is on the San Francisco Bay Area and northern California. But its ultimate aim is to document the growth of molecular biology as an independent field of the life sciences, and the subsequent revolution which established biotechnology as a key contribution of American science and industry.

UCSF Library, with its strong holdings in the biomedical sciences, is a collaborator on the archival portion of the Program. David Farrell, Bancroft's new curator of the History of Science and Technology, serves as liaison. In February 1998, Robin Chandler, head of UCSF Archives and Special Collections, completed a survey of corporate archives at local biotechnology companies and document collections of Berkeley and UCSF faculty in the biomolecular sciences. The ultimate aim is to ensure that personal papers and business archives are collected, cataloged, and made available for scholarly research.

Project Structure

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

Primary and Secondary Sources

This oral history program both supports and is supported by the written documentary record. Primary and secondary source materials

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

provide necessary information for conducting the interviews and also serve as essential resources for researchers using the oral histories. They also orient scholars unfamiliar with the field or the scientist to key issues and participants. Such orientation is particularly useful to a researcher faced with voluminous, scattered, and unorganized primary sources. This two-way "dialogue" between the documents and the oral histories is essential for valid historical interpretation.

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

Oral History Process

The oral history methodology used in this program is that of the Regional Oral History office, founded in 1954 and producer of over 1,600 oral histories. The method consists of research in primary and secondary sources; systematic recorded interviews; transcription, light editing by the interviewer, and review and approval by the interviewee; library deposition of bound volumes of transcripts with table of contents, introduction, interview history, and index; cataloging in national on-line library networks (MELVYL, RLIN, and OCLC); and publicity through ROHO news releases and announcements in scientific, medical, and historical journals and newsletters and via the ROHO and UCSF Library web pages.

Oral history as an historical technique has been faulted for its reliance on the vagaries of memory, its distance from the events discussed, and its subjectivity. All three criticisms are valid; hence the necessity for using oral history documents in conjunction with other sources in order to reach a reasonable historical interpretation.¹ Yet these acknowledged weaknesses of oral history, particularly its subjectivity, are also its strength. Often individual perspectives provide information unobtainable through more traditional sources. Oral history in skillful hands provides the context in which events occur-- the social, political, economic, and institutional forces which shape the course of events. It also places a personal face on history which not only enlivens past events but also helps to explain how individuals affect historical developments.

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

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

Emerging Themes

Although the oral history program is still in its infancy, several themes are emerging. One is "technology transfer," the complicated process by which scientific discovery moves from the university laboratory to industry where it contributes to the manufacture of commercial products. The oral histories show that this trajectory is seldom a linear process, but rather is influenced by institutional and personal relationships, financial and political climate, and so on.

Another theme is the importance of personality in the conduct of science and industry. These oral histories testify to the fact that who you are, what you have and have not achieved, whom you know, and how you relate has repercussions for the success or failure of an enterprise, whether scientific or commercial. Oral history is probably better than any other methodology for documenting these personal dimensions of history. Its vivid descriptions of personalities and events not only make history vital and engaging, but also contribute to an understanding of why circumstances occurred in the manner they did.

Molecular biology and biotechnology are fields with high scientific and commercial stakes. As one might expect, the oral histories reveal the complex interweaving of scientific, business, social, and personal factors shaping these fields. The expectation is that the oral histories will serve as fertile ground for research by present and future scholars interested in any number of different aspects of this rich and fascinating history.

Location of the Oral Histories

Copies of the oral histories are available at the Bancroft, UCSF, and UCLA libraries. They also may be purchased at cost through ROHO.

Sally Smith Hughes, Ph.D.
Research Historian

Regional Oral History Office
April 1998

Oral Histories on Molecular Biology and Biotechnology

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

William J. Rutter, Ph.D., The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco, 1998

In Process

Paul Berg, Ph.D.

Herbert W. Boyer, Ph.D.

Niels Reimers

Robert Swanson

Keith R. Yamamoto, Ph.D.

INTRODUCTION by Joshua Lederberg, Ph.D.¹

For the Love of Enzymes: The Odyssey of a Biochemist is not the book that Arthur Kornberg originally intended. His first drafts were focussed on an exposition of the facts of biochemistry he felt should be more widely learned by the general public. His friends and admirers sought to persuade him of the legitimate interest in a biography of a science, in its day-to-day challenges, in the development and personal character of its practitioners, in the interplay of innate and environmental influences that may lead to extraordinary accomplishment. Gradually, almost grudgingly, the successive drafts of his manuscript have responded to that appeal: we now have a work that combines scientific exposition with autobiographical memoir. Kornberg has played such a commanding role in the biochemistry of the gene: it is impossible to tell its history and exclude the personality that brought so much of it about. The subject is at the very center of public expectations for the application of science to human understanding and benefit.

His story has no simple lessons. Its drama has little of the spice of interpersonal conflict, of any "race for the gold." His rivalry is with a reluctant Nature who demands ingenuity and perseverance before delivering the real prize, the secrets of how the world and its life are contrived.

My scientific acquaintances are almost evenly divided between those who were born with a passion for science, have been driven by an inner vocation, and those who came to it as a later discovery, perhaps even an accident. Kornberg belongs to the second category; it may be associated with the unflagging and methodical way in which he has pursued one accomplishment after another for four decades, and with more yet to come. He has always been deeply devoted to his family, with no noticeable decrement to his scientific productivity, and with a yield of

¹At Dr. Kornberg's suggestion, the interviewer asked Dr. Lederberg if we could reprint for this oral history volume his introduction to Dr. Kornberg's autobiography, For the Love of Enzymes. When Dr. Lederberg kindly agreed, the interviewer asked him to write additional comments on the interactions of the Stanford Department of Genetics, which Dr. Lederberg was recruited to chair in 1958, and the Department of Biochemistry, which Dr. Kornberg was brought in to head the following year. Again, Dr. Lederberg agreed, and also added a concluding paragraph on the biotechnology industry. Because the sections which were not updated differ from the foreword published in the Kornberg autobiography, this present introduction contains substantially new information. We are grateful to Dr. Lederberg for his time and effort.

companionship and laboratory collaboration with a gifted wife (the late Sylvie Kornberg) and three sons already exhibiting extraordinary scientific and professional achievement. That balance and moderation has characterized his administrative accomplishment in building a department of biochemistry whose productivity is unmatched, and one which gives the lie to the proposition that science today is achievable only with immense groups and huge machines, or that it demands a renunciation of other human values.

Kornberg's early life typifies a generation (like my own) of second generation immigrant Jews in New York City, the parents making great sacrifices to ensure an education for their children. Nothing in his home background pointed to science except the encouragement to study and to excel. The public schools reinforced that acculturation, the ideal that academic achievement would be a unique opportunity for social and economic mobility out of the sweatshops. City College in New York has nurtured a lion's pride of Nobel Prize winners; but it offered very little in the actual content of undergraduate scientific education (and in those days, none whatever at the graduate level). It did offer a talented, ambitious and competitive peer group that helped to sharpen the aspirations of its students, and a faculty that, whatever else, fed the sense of individual worth of each of them, notwithstanding attributes of race, color or economic class. The external world was not so receptive; there were few opportunities open to Jews in academic or industrial science. The professions such as medicine (however the medical schools might ration their admissions) at least offered a prospect that individual careers might depend on skill rather than belonging to the right clubs.

A decade later, it was the mobilization of the universities for training in the skills to be recruited for World War II that finally cracked those barriers (as shaped my own experience). Indirectly, the same process had opened up the National Institute of Health, and gave Kornberg (now a medical graduate and a naval ship's doctor) his first research opportunities. His interests meandered from jaundice to nutrition (as studied in rats) to what was his predestination, the isolation of enzymes. This foreword should not take the place of his text; and indeed better that it be read afterwards as well.

I first met Arthur thirty-five years ago, at the summer course given by van Niel where he "learned microbiology" in preparation for his taking that chair at Washington University. That was a fateful meeting, eventually leading to my joining him at Stanford five years afterwards.

I would indeed have preferred joining his new biochemistry department; but we have differences in how (or whether) we voice a philosophy of science, that he may have been wise to foresee from the point of our first meeting. It fell to me to join a fraternal order of basic science departments: Arthur's vision of how to maintain some

balance in the politics of the medical school executive committee, between the ideals of the sciences and of the clinical services, the latter also leveraged by their being the fount of much greater cash flows in one or the other direction. In its research programs, Genetics was hard to distinguish from Biochemistry. Indeed, as molecular biology attained its ascendancy, this became true as well of Pharmacology, Microbiology, even Anatomy (under the rubric of Structural Biology), Developmental Biology, and so forth. In its teaching, Genetics had the special role of fomenting an interest in populations, and how they evolve. That is, we sought to enlighten our understanding not just of how some biological system worked, but also how it had come about. This entailed a focus on mutation, how mutations affect development and phenotype, and the dynamics of selective forces that eventuate in evolutionary change. Recruiting Luca Cavalli-Sforza was to be the keystone of providing that intellectual oversight, joined for a time by Walter Bodmer, until he was lured by an Oxford professorship. Yet both of these giants have also spent much of their careers in a similar application of DNA analyses. Arthur and his group were to play a major role in providing the principal tools for that new molecular genetics.

Arthur's manifest approach to the choice of scientific problems is to focus on the small particular, to eschew large social or scientific goals, to set aside grand design and theoretical synthesis. He says "I have never met a dull enzyme." Less certain is whether this is good advice for anyone but an Arthur Kornberg, which is to ask whether he has truly followed it himself. If not by design, then by intuition, he has always managed to sight the central targets of biological enquiry in his "enzyme-hunting;" and his method has always embraced far broader issues than the mechanical steps of purification and isolation. He may be right that these are daunting to many impatient youngsters, and that enzymology is lamentably being bypassed by the more facile doctrines of gene-hunting. I agree with him that the thousand and odd enzymes involved in intermediary metabolism and nucleic acid and protein synthesis are the indispensable periodic table of biology. As with the chemical atoms in Mendeleev's time, only a small proportion of the enzymes we can infer have actually been isolated--and this is an arduous and indispensable task that must not be overlooked as the real work of mapping the human genome. But besides Kornberg's technical skills, we also need his taste in selecting those targets that warrant first priority. As he has always practiced, despite his preachments, we need to embed that knowledge of enzymes in a broader panoply of their functional relationships in the cell. This will require a host of other skills, like electron microscopy, NMR spectroscopy and X-ray diffraction, not to mention genetic analysis. Explanation in contemporary biology is chemistry; we need the purified components to reconstruct the cell as the final test of our analytical models. The essential prerequisite for all of this is his puritanical prescription: "isolate it!"

As the practical applications of molecular genetics became more evident, starting around 1970, Arthur was at first reluctant to play any part in the Biotechnology startups. He has written how his friendship and burgeoning business relationships with Alex Zaffaroni led to the most constructive of partnerships. The private sector could bring enormously more capital to bear, and could focus on achieving material results for public benefit--and when this happened to add pecuniary to psychic composition for the time spent. Biotechnology Alley had been an extrapolation from Silicon Valley, the consummation of Provost Fred Terman's dreams that the basic ideas from Stanford's physical and engineering sciences could fertilize brand new industries as important as Intel and Hewlett-Packard have become in the U.S. economy. The conjunction of intellectuals and entrepreneurs in the San Francisco Bay Area is unmatched anywhere, and was nucleated by the early emergence of forms like Syntex, Alza, Genentech, Cetus, now followed by an almost endless list. California's climate and natural beauty enhanced the attraction; and for a while there was enough vacant land to provide a garden for the startups at modest cost.

The modern era of DNA research began in 1944 with the discovery by Avery et al. that pneumococcal DNA could transmit heritable characters from one cell to another. For years, until about 1980, I was bemused with the question: given such a revolutionary discovery, how long will it take to reach practical medical benefit? The flowering of the biotechnology garden makes such questions foolish today, and are all indebted to Dr. Arthur Kornberg for achieving some of the most important insights that have led to that eventuality.

Joshua Lederberg, Ph.D.
Rockefeller University

July 1998
New York

INTERVIEW HISTORY--Arthur Kornberg, M.D.

This oral history with the Stanford biochemist and Nobel laureate Arthur Kornberg is one of a series tracing basic biomolecular science in northern California and its association with the rise of the biotechnology industry. Professor Kornberg himself has a foot in each camp. A steadfast advocate of biochemistry as the path to understanding fundamental biological processes, he could, despite his medical degree, be taken as the quintessential basic scientist. As any biochemist can tell you, his name is linked with early work on DNA replication, for which he was awarded the Nobel Prize in 1959. Eight years later, in 1967, he and his laboratory were first to achieve the artificial synthesis of viral DNA--"creation of life in a test tube", as the journalists to his displeasure headlined it. In short, he is a basic scientist of world stature.

Yet Dr. Kornberg, like so many of his colleagues in contemporary biology, has strong ties with industry. Most if not all of his associations were instigated by his friend Alejandro Zaffaroni, chemist, entrepreneur, and founder of several companies based on technologies first developed in academic biology. One of the first of these was ALZA--Zaffaroni's company in name as well as actuality--for which Professor Kornberg became a scientific consultant in 1968. He recounts in the oral history how this introduction to industry led to deeper commercial involvement in 1980. In that year, Zaffaroni persuaded Dr. Kornberg, who in turn persuaded his Stanford colleagues Paul Berg and Charles Yanofsky, to join him in founding DNAX, a biotechnology company located in Palo Alto, adjoining the Stanford campus. Dr. Kornberg currently is a member of the scientific advisory board of this and several other companies. At eighty, having outlived two accomplished wives, he continues to keep a regular schedule in his Stanford laboratory where he and his students pursue research on the enzyme polyphosphate. Thus in effect he is a man of both the academic and commercial worlds.

Dr. Kornberg has published an autobiography, For the Love of Enzymes, and The Golden Helix, his history of DNAX.¹ There is also a 36-carton collection of his personal papers in Stanford's Green Library. With extensive information available, one might well ask, why the need for an oral history? The answer is that the three types of documents--

¹ For the Love of Enzymes: The Odyssey of a Biochemist, Cambridge: Harvard University Press, 1989; The Golden Helix: Inside Biotech Ventures, Sausalito, California: University Science Books, 1995. Although the latter gives brief treatment to Genentech, Amgen, Chiron, and Regeneron, the major focus is DNAX.

the books, the papers, and the oral history--are complementary, yet distinct, differing in both substance and tenor. Dr. Kornberg's two fine books tell a story deliberately limited to his endeavors in science and business; he writes a little about personality, less about context. Like his approach to scientific research, his style is focused and spare. His correspondence in the Stanford archives is that of a scientist deeply engaged in his work, reluctant to write more than necessary to get the point across. He does not make letters occasions for digression into personality, politics, and the circumstances surrounding his science. Therefore, an oral history capturing a more informal and discursive Professor Kornberg and his institutional context, particularly that of Stanford University and the Department of Biochemistry, was well warranted.

It was for the purpose of forming and directing a new department of biochemistry that Dr. Kornberg came to Stanford in 1959, the year that its medical school was moved from San Francisco to the Palo Alto campus. The idea was not only to unite all aspects of the medical curriculum (the first two years had been taught in Palo Alto and the two clinical years, in San Francisco) but also to encourage interchange between the basic and clinical sciences. Kornberg and the Department of Biochemistry were key ingredients in this program, all the more so when Kornberg was awarded the Nobel Prize a few months after his arrival.

There is much in the oral history about the department's organization, earliest faculty (which came almost to a man--and one woman--from Kornberg's lab at Washington University, St. Louis), and characteristics--small size, insularity, and communal social and financial structure. There is also discussion of wider contextual issues, notably the recombinant DNA debate of the 1970s and the subsequent commercial application of the recombinant DNA and cloning science to which Stanford scientists made seminal contributions. Of particular interest is Arthur's commentary on the controversy surrounding DNA polymerase I research of the 1950s, for which he received the Nobel Prize. Also significant is his adamant opinion that the biochemistry department provided the building blocks for recombinant DNA science and yet largely missed its potential for practical application. Instead of Stanley Cohen in Genetics at Stanford and Herbert Boyer at UCSF, he credits Peter Lobban, a Stanford graduate student in biochemistry in the late 1960s and early 1970s, for recognizing the commercial potential of recombinant DNA technology: "I believe, without historical research on this, that he [Lobban] was the first and clearest exponent of this technology and its applicability."

The discussion of DNAX reflects Kornberg's selective enthusiasm for the commercialization of biology that the biotechnology industry represents. He speaks with respect of the corporate executives of Schering-Plough, the American pharmaceutical company that bought DNAX in 1982. But he also provides insights into tensions and resolutions at

several levels--between scientific research and commercial production; between DNAX scientists and advisors, and Schering-Plough management; between DNAX and competing biotech companies; between molecular biologists and biochemists within DNAX.

The oral history also describes a scientific style that places enzymes--clean enzymes and clean substrates--at the center of laboratory endeavor in biomedicine. "It was the classical tradition of enzymology," Dr. Kornberg remarked, "that led me to DNA polymerase and DNA ligase and the other reagents without which there would be no recombinant DNA." The interviews suggest that his exacting standards for science might possibly spill over into lifestyle. He comments, for example, on his preoccupation with the efficient use of time, and reluctance, until recently, to leave the laboratory in order to travel and give talks. One watches between the lines of the oral history an individual living up to his own high standards--in science and every other aspect of life.

The oral history is organized around three themes: the Department of Biochemistry, Dr. Kornberg's research at Stanford, and DNAX. He describes the department's transformation from a pure basic science enterprise into one with increasing ties with industry, through its Industrial Affiliates Program, consultantships, and faculty member equity in corporate concerns. The department's history reflects the gradual commercialization of biology, a process now pervasive in American universities.

The Oral History Process

At an initial meeting on January 7, 1997, Professor Kornberg and I discussed how best to orient the interviews around pre-existing material, particularly the two books mentioned above. Because For the Love of Enzymes provides a full account of his upbringing and education, we decided to begin the interviews with an overview of his work at Washington University in order to provide the context for his move to Stanford in 1959 and his continuing research on DNA replication. The reader seeking full treatment of this earlier history will wish to refer to these published sources and to Dr. Kornberg's collected papers.

The six interviews conducted between March and May, 1997, are based on the interviewer's extensive research in Dr. Kornberg's papers in Stanford's Green Library as well as those on DNAX, stored in his laboratory, which he kindly made available to me. Although some duplication of existing accounts was inevitable, this oral history provides substantial new information and a more spontaneous and expansive historical view. A cordial but careful informant who chooses words carefully, Dr. Kornberg warmed to the interview process, eventually allowing himself digressions and personal asides. I suspect

he was pleased and somewhat surprised to learn that I had found his personal papers to be a rich historical source. Fit and youthful for his near-eighty years, he was a joy to work with, supplying documents--and on one occasion a hand-packed lunch--to support the interviews and interviewer.

The edited transcripts were mailed to Professor Kornberg for his review; he made careful additions but did not substantially change the tenor or content. Characteristic of his efficiency, he returned the transcripts before my deadline. The oral history stands as testimony to one man's vision of the ideal institutional base for biochemical research--the Stanford Department of Biochemistry, single-minded dedication to science, and to the fruitful alliance that can--and has--been forged between academia and industry.

I wish to thank John Wilson, M.D., who is writing a history of Stanford Medical School and who supplied background information on the school; Margaret Kimball and Heidi Heilemann, archivists at Stanford Libraries, for providing access to and assistance with, respectively, Green Library and Lane Medical Library archives; and to Beverly Forsyth, Dr. Kornberg's devoted assistant, who supplied documents and conveyed messages.

The Regional Oral History Office was established in 1954 to augment through tape-recorded memoirs the Library's materials on the history of California and the West. Copies of all interviews are available for research use in The Bancroft Library and in the UCLA Department of Special Collections. The office is under the direction of Willa K. Baum, Division Head, and the administrative direction of Charles B. Faulhaber, James D. Hart Director of The Bancroft Library, University of California, Berkeley.

Sally Smith Hughes, PhD
Research Historian/Senior Interviewer

April 1998
Berkeley, California

Regional Oral History Office
Room 486 The Bancroft Library

University of California
Berkeley, California 94720

BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

Your full name Arthur Kornberg

Date of birth March 3, 1918 Birthplace Brooklyn, New York

Father's full name Joseph Kornberg

Occupation Merchant Birthplace Poland

Mother's full name Lena Kornberg

Occupation Housewife Birthplace Poland

Your spouse Widowed

Occupation ----- Birthplace -----

Your children Roger - Thomas - Kenneth

Where did you grow up? Brooklyn, New York

Present community Portola Valley, California

Education B.S. - City College of New York

M.D. - University of Rochester

Occupation(s) Professor, Department of Biochemistry

Stanford University School of Medicine

Areas of expertise Biochemistry

Other interests or activities Writing, Lecturing, Travel

Organizations in which you are active -----

I EARLY CAREER AT THE NATIONAL INSTITUTES OF HEALTH¹Research in Nutrition

Hughes: Dr. Kornberg, because you have so fully covered your upbringing and education in your autobiography,² we are not going to focus here on those aspects of your life. But I would like to hear a little about your early career. Your early research fell under the rubric of biochemistry, did it not?

Kornberg: Well, not in my first three years [1942-1945] as a nutritionist at NIH. As you know, I never earned a Ph.D. in biochemistry.

Hughes: But you were doing biochemical research, right?

Kornberg: Well, it would have been regarded as biochemical in some contexts of nutrition. The group at the NIH was not at the vanguard of the new nutrition, that is, working with microorganisms rather than rats.

When I went to work with Severo Ochoa in 1946, enzymology was utterly new to me. That was my introduction to genuine biochemistry and enzymology, and from then on that was all I was interested in and wanted to do.

Hughes: Is that when you really got hooked?

Kornberg: Yes, it is fair to say that. I was already uneasy with nutritional research in '45, getting bored with feeding rats and not understanding what was going on inside the rat. At the

¹ To achieve better chronology, the transcripts as they appear in this volume do not always follow the order in which the discussion was recorded.

² Arthur Kornberg. For the Love of Enzymes: The Odyssey of a Biochemist. Cambridge, Mass.: Harvard University Press, 1989. Hereafter, Enzymes.

end of the war--that was the summer of '45--Bernard Horecker, who was a good friend, returned to biochemistry in which he had taken his degree. So I apprenticed myself to him, and he taught me how to make some enzyme preparations and so forth. We began planning where I would go if I could persuade the authorities at NIH to let me go somewhere to learn the new biochemistry.

Hughes: Was that what people called it, the new biochemistry?

Kornberg: It was certainly new to me because I hadn't learned it in medical school. It was certainly new to my advisors in nutrition, but not new to people who came from Europe, and to people who were trained in a few laboratories, such as [Carl] Cori's laboratory at Washington University in St. Louis or [Hans T.] Clarke's at Columbia or Harland Wood's, not yet at Western Reserve University. There were pockets of people doing enzymology or dynamic biochemistry, for example, at Wisconsin. A textbook of the time, Dynamic Aspects of Biochemistry, by Ernest Baldwin,¹ described the state of the science.

Hughes: Nothing had come out of the Cambridge School?

Kornberg: Baldwin was from the Cambridge School, but all was destroyed during the war.

When I convinced NIH to sponsor my trip to a laboratory, I thought first of David Keilin's. But I was told that his lab really wasn't functioning well as an aftermath of the war. One of the American refugees from Cambridge, David Green, invited me to his lab, but I had friends who said David was a difficult character.

Mentors

Kornberg: There was a young Spaniard, Severo Ochoa, working at New York University Medical School. Actually, he was a guest in the Biochemistry Department; he was doing some interesting work. Bernie Horecker and I read his papers and found that he was doing the kind of enzymology we'd love to do. So I applied to work with him. He had nobody else so he took me. I was still in uniform.

¹ New York: Macmillan Co., 1948.

There was no housing in New York. My wife Sylvy and I had to move from one hotel to another every few days, until we found an apartment saved for us by Herman Kalckar. Those were such eventful, exciting years; I learned something new every day. I wasn't doing anything important experimentally, but I was acquiring scientific language and attitudes. Ochoa was a very impressive person, with his enthusiasm, optimism, and his breadth of vision. You may know that in later years he was among the most celebrated people in Spain. Don Severo and King Carlos; Juan Carlos and Severo--they were actually good friends.

That year with Ochoa was absolutely great; every day mattered. Ever since, I've told my students and people working with me, "Hey, you wasted an afternoon; it will never come back." I have always been preoccupied with time. Time mattered. Every hour mattered. There was an exhilaration with discovery. I could get a fact, or fail to find a fact, in a matter of minutes or hours, rather than waiting for months as in research with rats, or in humans to sort out a very muddled set of circumstances presented by a patient.

Hughes: So it was precision as well as time saved which appealed to you?

Kornberg: Control. I had the authority to impose certain conditions that were well enough controlled that I could decide I'd either learned something or didn't.

And then things did go well. There was so little known at the time that no matter what you did, you'd discover something exciting. Or so it seemed.

Hughes: Did you feel that you were on the crest of a new wave?

Kornberg: I had confidence that my association with Ochoa gave me access to, familiarity with, those who were identified as being at the forefront of biochemistry. I felt that I knew what they were doing and that I was capable of doing something along those lines. I was confident that, if I worked hard and did things carefully, I would find something worthwhile. When we come to discuss, as I think I frankly did in my book,¹ how we discovered this utterly novel enzyme DNA polymerase I that is the basis for heredity, it was not done with a vision that I would discover such a key enzyme. It was more my love of enzymes and

¹ Enzymes.

always wanting to tackle something at a point of difficulty beyond what I had done before.

Hughes: So you were pushing yourself a little each time as a scientist.

Kornberg: Always, always--looking for trouble. [laughs] I think the essence of science is that you don't sit back and say how great this finding is. You say, "Gee, this tells me I don't understand this." Or, there is another opportunity. "Can we use our methods and ingenuity and drive to find the enzyme that does something that hasn't been done before?"

Hughes: Are there people besides Ochoa that you consider to be mentors?

Kornberg: There are those I knew personally and others I admired from the literature.

Ochoa gave me the opportunity to learn about enzymes. I was impressed by him; he had endured so much. He had been through wars and revolutions in Spain and Germany and England. And in New York he was in the most tenuous of positions. There was a sublime air about him--intense interest in the science, not seeming to worry about what would happen the next day, an enthusiasm for the results, even if they weren't that interesting.

Did I learn that from him; I don't know. I have a similar attitude. Could I have learned something like that? I don't think so. I haven't been able to teach it to anybody. So you can say that you're born with it or you have it, and then you are reinforced by seeing it practiced by somebody whom you admire. The other thing I learned was that I didn't think Ochoa was that much smarter than I was. I thought I could achieve what he had.

Cori was something else again. Cori had extraordinary intellect and breadth of knowledge and was awesome that way. And yet he was so supportive of what I was doing that I was encouraged by his respect and confidence in me. So in that sense he was also a mentor.

There are giants in the literature, like Otto Warburg and others... You learn from everybody; you learn from your students and colleagues all the time. I can't believe the patience that my students have. They should be discouraged by repeated failures and the arduous nature of experiments and yet they go on. That's great.

II CHAIRMAN, DEPARTMENT OF MICROBIOLOGY, WASHINGTON UNIVERSITY
SCHOOL OF MEDICINE, ST. LOUIS, 1953-1959

Decision to Leave the National Institutes of Health [NIH]

Hughes: Dr. Kornberg, I want to go back to 1959 or perhaps even earlier to establish the context for Stanford's overtures to you to become chairman of the newly created Department of Biochemistry.

Kornberg: Yes, we should go back well before 1959. The department as it was constituted at Stanford in 1959 was really assembled at Washington University in St. Louis beginning in 1953. It might be appropriate to start there.

In 1952, I was at the NIH, very comfortable, and my work was going exceedingly well, or at least I thought so. Then I was approached by some very eminent people, Carl Cori and Oliver Lowry, at the Washington University School of Medicine to consider the chairmanship of the Department of Bacteriology and Immunology, renamed Microbiology. There were two elements that led me to accept their offer. I was becoming disillusioned with the less-than-inspiring administration of the NIH, and I was at the level where I had to intersect with them. Secondly, the NIH was building its Clinical Center and I thought that this was ominous because the basic science that was dominant at the NIH would now become very clinically and practically oriented.

I was attracted by the flattering invitation from Washington University and the association that I would have with some of the great scientists in medical science--Carl and Gerti Cori, and others. And so in mid-1952 I decided to accept their offer and appeared in St. Louis in January of 1953. As events turned out I had misjudged the situation. I inherited dismal, medieval laboratories which became my responsibility to rehabilitate. As a member of the executive committee, I looked

forward to the opportunity to discuss science and education. Rather, there were debates about nurses' salaries and things like that. It was no more inspiring administratively than it had been at the NIH.

Then something occurred I hadn't counted on. In 1952, I had four applications for postdoctoral work from people who later became eminent in science, but were reluctant to go to St. Louis. Their interest in me was genuine, but they were also interested in being at the NIH. So three of them found alternative sponsors at the NIH. They were Bruce Ames, Ed Korn, and Gordon Tomkins, who before his premature death [1975] in a surgical procedure, was one of the people who rejuvenated the UC San Francisco Department of Biochemistry.¹ The fourth was Paul Berg, and I'll come back to him in a moment.

I often wondered in the succeeding years whether I had made a great blunder in moving from the NIH, where I was so comfortable, had such excellent facilities and things were going so well; the academic heaven in St. Louis never materialized. Nevertheless in 1953, I became chairman of a department dealing with subjects in which I had no special knowledge. I was not a microbiologist or a bacteriologist or an immunologist.

Cornelius B. van Niel's Course in General Microbiology

Kornberg: That summer I arranged to come to California to take a course that became legendary. It was a course given to twelve people every summer at Stanford's Hopkins Marine Station. The alumni of that course became a who's who in science, including chemists as well as biologists.

Van Niel was an extraordinary figure and a teacher of the kind that one never finds anymore. He could lecture for eight hours a day and enthrall you with accounts of heroes and villains in science; the Dutch microbiologists were always the heroes. He wouldn't mention any pathogenic organism or the host's immune system. The course in general microbiology was

¹ For more on Tomkins and the rejuvenation of UCSF biochemistry, see the oral histories with Herbert W. Boyer, William J. Rutter, and Keith R. Yamamoto in the UCSF Biotechnology Oral History Series. Hereafter, UCSF Biotechnology Series.

inspiring and enlightening but not suitable to teach medical students I would face in September.

Hughes: He was teaching people who were then going to apply the information in basic research--was that the idea?

Kornberg: Yes, I would think so. He was on the Stanford faculty, and the Hopkins Marine Station still is a branch of the biological sciences department.

Teaching Microbiology to Medical Students

Kornberg: In September of 1953, we were confronted with teaching bacteriology to 120 medical students in their second year. The remnants of the previous department, two or three people, taught old-fashioned bacteriology in which you carry out certain procedures to determine the bacterium by staining or some other means. The focus was on the pathogenesis of the disease for which the particular bacillus or coccus is responsible. When I listened to a few of the lectures, it was apparent how inappropriate it was to teach microbiology in these very narrow practical ways. I was accustomed to the old orientation from having been a medical student, but that was fifteen years earlier and I was now imbued with biochemistry and genetics.

Hughes: And you had been exposed to van Niel's approach--

Kornberg: --as a general microbiologist. He was neither a biochemist nor a geneticist, but a good general microbiologist. My recruiting of new faculty was in the direction of introducing the modern aspects of biochemistry and genetics into microbiology.

Hughes: Had you been recruited with that understanding?

Kornberg: No, but there was no deception. My patrons there and particularly Carl Cori, the most distinguished member of the faculty, knew that I was a biochemist and what I wanted to do in research. As far as teaching was concerned, well, it would take care of itself.

After a year or two of teaching, the students, who had taken biochemistry in their first year, dubbed our course Biochemistry II. It was not well received. A fifth column of several people left over from the old department would tell the students that they weren't learning medical bacteriology and

were being deprived of exposure to information about syphilis and other diseases that would be crucial to becoming legitimate M.D.'s. [chuckles]

I might say as a postscript that in subsequent years the students we had those years, either practicing M.D.'s or in academic medicine, would refer to that course as the most memorable and enlightening course that they had had. That was due not only to the curriculum, but also to the spirit of the young people who were teaching the course. They were teaching subjects that they hadn't known anything about, but were learning it with novel insights.

Hughes: Did you have a model for the curriculum?

Kornberg: That's the point; there was no model; we had was no textbook. The famous textbook by [Bernard] Davis and co-authors came out only years later. We had no book the students could consult to capture this new attitude about the importance of biochemistry and genetics for learning about microbes, whether they were "good" or "bad" microbes.

Hughes: Didn't student attitude run counter to the basic science tenor you were trying to establish in the department?

Kornberg: Yes, and it's still true. Medical students by and large want to learn what they need to know to practice medicine, and they are not disposed to learn about photosynthesis or the scientific method. They don't want to spend time unnecessarily on subjects that aren't going to be tested on the national medical specialty boards. Medical students are not graduate students in the sense of wanting to increase their fund of knowledge and expertise and basic techniques. It is common now to introduce them to clinical applications of biochemistry. Things were even worse at that time.

Hughes: On the other hand, you shared medical experience with them; you are a physician who has turned to basic science.¹

Kornberg: Yes, but reactionaries can be less tolerant than other people, once having seen the light. I could see the importance of basic science, but couldn't convey it.

In fact, after two or three years in St. Louis, I wrote a memo to the dean of the medical school--it could have been Carl

¹ Dr. Kornberg received an M.D. degree from the University of Rochester in 1941.

Moore--proposing that instead of having students who wanted to be sports medicine doctors and private practitioners, we should appeal to those who want a school to prepare them for a career in academic and research medicine, without diminishing their capacity to practice medicine. My memo was ignored. It was considered almost suicidal that a school distinguish itself by focusing on the science in medicine. I think that would be true even today.

Now of course we have NIH medical scientist training programs. The NIH demands that students in the program be candidates for the Ph.D. as well as the M.D. Stanford prides itself on the fact that there are many research opportunities for all medical students. Perhaps two-thirds or three-quarters of them take advantage of these opportunities, some for financial reasons (because they get stipends for it), and others because the experience looks good in their curriculum vitae.

Members of the Department

Kornberg: The first person to join the department at St. Louis, who came with me from NIH, was a postdoc, Osamu Hayaishi. He was my first appointment as an assistant professor. After a couple of years he went back to the NIH in a scientist position, and a few years later became professor of biochemistry at Kyoto. He is the doyen of biochemistry in Japan, invited repeatedly by the emperor for his wisdom in science. He is both a great scientist and great statesman, and for many years the most eminent biomedical scientist in Japan. Osamu, before joining me, was very much involved in enrichment culture work, discovering soil bacteria with specialized metabolic capacities.

Also joining me later in 1953 was Paul Berg. He told his mentor, Harland Wood, at Western Reserve University that he did not want to work with Carl Cori, because he didn't want to go to St. Louis. His first postdoctoral year [1952] was with Herman Kalckar in Copenhagen. When he got my letter saying that I was moving to St. Louis, he agreed to come there. That was a momentous choice, because we've been close colleagues and friends ever since. He is not only bright and inventive, but also a very good citizen, a "boy scout."

As a young postdoc, Paul was willing to do some of the teaching in microbiology. We divided up the pertinent

subjects. He took some pathogenic bacteria and I took bacteriophages (bacterial viruses), about which I also knew nothing. Teaching that course proved to be instrumental in my later discovery of DNA polymerase. I became curious about the growth of the phages and how they replicated their DNA.

My next appointment was Melvin Cohn, who later became a founding member of the Salk Institute. Mel had been in Paris with [Jacques] Monod and [François] Jacob and was highly regarded by them. He was recommended to me as an exceedingly bright and effervescent person who knew microbiology.

In 1955, a postdoc, Robert Lehman, came. We became closely attached. I'm mentioning the people who would eventually become part of the faculty of the Stanford biochemistry department. Bob was one of the major figures in the purification of the system that revealed DNA polymerase, an enzyme unlike any other because it took directions from a template. No enzyme was known which could make a product with instructions from its substrate. Bob was exceedingly important in all that early work. He too lectured in the microbiology course.

The two or three people who had been in the department before I came left. None of them had held appointments with tenure. It was clear that that department had been languishing for a number of years. Appointments were reserved so that a new chairman could come in and fill the slots with freedom to develop a truly new department.

Then we recruited David Hogness. (He has just won a major prize, a consolation for not having gotten the Nobel Prize last year, something he richly deserved.) Dave had been with Mel Cohn, Jacques Monod and François Jacob in Paris, and before that at Caltech both as an undergraduate and graduate student. He was an outstanding student, working on bacterial metabolism, genetics, and biochemistry. After Paris, he had taken a job with Bernard Davis at New York University, but was unhappy there for various reasons. With Mel Cohn's advice and my choice, he came to St. Louis. His share in the teaching was microbial metabolism with proper attention to the pathogenic microbes.

We needed virology, and recruited Robert DeMars, who is now at the University of Wisconsin. When he left to fulfill his military service, we got Dale Kaiser, once again a postdoc in the Monod-Jacob group in Paris. At that time the Paris group was the world's most eminent in microbial genetics. Both Monod and Jacob, and to some extent [André] Lwoff, their mentor, were

recognized as the most brilliant in aspects of microbiology that would become molecular biology. So, we had three people who had come directly from that mecca of science.

Hughes: Why did they want to come to Washington University?

Kornberg: I can't be sure.

There was one person we tried to recruit but failed. Peter Geiduschek. He has since become an outstanding scientist at UCSD [University of California, San Diego]. He is a physical chemist. I was attracted to him because he would bring physical chemistry to the department. But he declined and later confided that he regretted not joining us.

Before inviting Dale Kaiser, I had invited Gordon Lark, but he said it would be another year before he could come. I felt we couldn't afford to wait, so we went to Kaiser. I have gathered from Gordon that he too was sorry not to have become part of a congenial and productive group. Then a very brilliant scientist, Jerard Hurwitz, joined my group as an instructor or assistant professor.

Hughes: Had the medical school at Washington University decided that its effort should take on a more basic science orientation?

Kornberg: There was a strong legacy of basic science at the group. Carl Cori, Joseph Erlanger, and Herbert Gasser, and many others in the medical school, were distinguished in the basic biomedical sciences. Washington University at that time was arguably one of the top medical schools in basic science. To this day, it remains one of the top medical schools. It has suffered from the fact that it is named Washington University, confused with George Washington University and the University of Washington.

Hughes: How did you think of yourself in St. Louis?

Kornberg: Oh, as a misfit. [laughter] I had no credentials in microbiology or being a Midwesterner.

Hughes: So you weren't yet thinking of yourself as a biochemist?

Kornberg: I did. I wanted to explain why biochemistry was essential for the teaching and practice of microbiology. But as I said, there was no textbook at the time that validated that approach. The students were very unhappy because ours was a novel, unorthodox, and possibly wrong approach to medical microbiology. We had no textbook, no tradition, no precedent.

One of the reasons I was happy to move to Stanford was to teach biochemistry rather than microbiology.

Hughes: Did the focus of the department at St. Louis gradually broaden?

Kornberg: No, it actually narrowed to DNA and nucleic acids. People joined the department who had really never heard of DNA. DNA was quite novel then. In the late 1940s and early 1950s, geneticists had not accepted that DNA is the genetic material. They didn't trust the work of [Oswald] Avery, who had shown that genes are DNA, and prominent people refuted it. Most thought that proteins had to be the genetic material.

Erwin Chargaff and Base Pairing

Kornberg: As late as 1956, three years after the Watson-Crick publication on DNA structure, which had credibility and celebrity everywhere, Chargaff, an eminent biochemist, presented a paper at a major symposium in Baltimore on the chemical basis of heredity. He ridiculed the double helical structure and stated it had no significance. Ten years earlier, he used the newly found paper chromatography technique to show the equivalence in DNA of A [adenine] to T [thymine] and G [guanine] to C [cytosine].

Yet in 1956, he still didn't accept the fact that there is base pairing, the lock and key relationships of A and T and of G and C. Later, when it became so commonplace that it was newspaper text, he claimed to have discovered base pairing. He never did. Some people deplore the fact that Chargaff never got a Nobel Prize for his discovery. But he rejected the significance of base pairing long after it was accepted by everyone else.

Hughes: So Chargaff originally talked about the equivalence--

Kornberg: He talked about the equivalences. It was a phenomenon but not understood. In all DNAs, A's equal the T's and the G's equal the C's. He also pointed out that in different species, the number of A-T pairs versus G-C pairs can vary from a ratio of 0.5 to 2.

Hughes: He didn't suggest the concept of base pairing?

Kornberg: He rejected it, three years after the base-paired structure of DNA had been proposed and accepted by everyone else.

Hughes: In the paper published before 1953?

Kornberg: He simply described base-pairing as an interesting feature of DNA. He didn't know its structural significance and certainly didn't understand its biological significance, that base-pairing is the basis for replication.

Early Work On Nucleotide Chain Synthesis

Hughes: Were you originally taken in by the protein hypothesis concerning gene structure?

Kornberg: No, I was quite remote from it. I freely admit that when the Watson-Crick paper came out, I was not electrified by it, as I should have been.

Hughes: Why weren't you?

Kornberg: I was so focused on enzymology, on how enzymes work, that to this day I joke about it. I was ambitious enough to want to know more about the enzymology of nucleic acids from the bottom up; how each building block is made. I spent five years trying to determine the true building blocks and how they are made. Then, how are they assembled into DNA? I shouldn't say I'm proud--but I am appreciative that my contribution, along with those of others, defined the pathways of how you make the building blocks. Virtually all drugs used in the treatment of cancer, AIDS, herpes, autoimmune diseases, are designed to interrupt those pathways. Our basic studies proved to have great practical value--but I didn't know that then or anticipate it.

I was inspired by the work of Carl and Gerty Cori on glycogen and starch, polymers of glucose units. I hoped that I could do the modest thing of extending chains of nucleotides as we find them in RNA or DNA. The first work I did was on RNA. We made an important discovery that we didn't fully understand, and then we blew it.¹ [interruption]

That is another story but not irrelevant because it wasn't DNA that I was after as much as knowing how a chain of nucleotides is made. Actually, I approached the problem in a roundabout way. The phosphodiester linkage found in RNA and

¹ See Enzymes, pp. 148-151.

DNA is also found in another class of compounds, the phospholipids. I studied them because I thought that if I could understand how that linkage is made in a simpler and more accessible molecule, then I might understand how it is made in the chains of DNA and RNA.

My interest in nucleic acids goes back to 1950. Yet when the DNA structure was announced, it interested me but didn't alter my research or give me new vistas. When I was disappointed that my discoveries with RNA had been preempted by Ochoa, I said, Well, I've made some observations about the synthesis of DNA; let's go back to DNA. But I have to admit it wasn't because DNA is the central molecule in heredity. I appreciated that it was, but what inspired me was the enzymology of lengthening chains of preexisting DNA.

DNA as the Genetic Material

Hughes: Had you been convinced before [James] Watson and [Francis] Crick that DNA was the prime molecule in heredity?

Kornberg: I was not involved in that debate. In defense of biochemists, I recall Gerty Cori telling me in 1947 that the Avery paper was a very important paper. Yet in the mecca of genetics at Caltech in 1952, [Max] Delbruck and others didn't appreciate its significance even eight years later.

Hughes: What was your reaction to Gerty Cori?

Kornberg: She was a very volatile and inspiring person, a fascinating person, truly a great scientist.

Hughes: Watson and Crick established the dogma that DNA was the hereditary material?

Kornberg: No. In 1952, it was a member of the [Max] Delbruck [bacteriophage] "church", Al[fred] Hershey, who did a rather crude, but telling experiment. He showed that what was transmitted by a phage to generate its progeny was not the protein coat but rather its DNA. The interpretation of the Hershey experiment turned out to be correct.

Hughes: Why wasn't the experiment impressive?

Kornberg: It was crude; some protein was also injected into the cell, and it wasn't very quantitative. The results were predictive of

more elegant experiments. I was probably aware of them but no more so than of the paper by Watson and Crick. So I can't claim to have had the inspiration from those discoveries that then led to my discovery of the enzyme that makes DNA. It was a great stroke of fortune that I did and Bob Lehman figured prominently in that research because he was the postdoc; we worked very closely together.

Hughes: Could some of this be due to the division between the biochemical and biological sciences that you referred to? The phage group was composed mainly of biophysicists and biologists, not biochemists.

Kornberg: You are right. There were great intellects from physics who went into biology and thought they could solve problems by the power of their intellect. I'm critical to this day of some of the physicists who entered biology to solve biological problems--some called biophysicists. I am critical of their disinterest and contempt for chemistry.

Some physicists are dismissive of chemistry as messy stuff. But unfortunately for them, life processes are chemical. [laughter] You've got to get through the chemistry. You can't do quantum mechanics in enzymology; you may not be able to for another fifty years. What someone called the mumbo-jumbo of biochemistry is at the heart of the matter.

Hughes: But does the lack of communication cut both ways? You were focused on enzymological problems; you didn't have a great incentive to read the literature of the phage school.

Kornberg: Well, yes and no. Lehman joined me as a postdoc, and he was trained in phage biology. Dale Kaiser came and was one of the leading lights in phage biology and genetics.

Hughes: So they were following phage biology.

Kornberg: Yes, and they were doing it. When I decided to teach an element of microbiology, I chose phages as the topic for discussing virology with medical students. I wasn't as dumb as I make out. I was very inspired as a medical student by the spectrum of life from inorganic matter to the very simple plant viruses--tobacco mosaic virus. It's a molecule; is it living or not? I had heard inspiring lectures that showed a continuum of life from the simple to the more complex viruses to the simple bacteria and so on. There was no division--I had a good sense of that.

Also, when I was in nutrition, I heard Ed Tatum give a seminar on his Neurospora work: one gene as the source of information for one enzyme. I was greatly inspired by that. It didn't affect my work, but much more than most people in nutrition I was absorbing things. But in my work I was always focused; I would say, Well, that's great to learn, but this is the next thing I have to do in my research.

Jacques Monod and DNA Polymerase

Kornberg: Jacques Monod, who is one of the great luminaries in the modern science which was to become molecular biology--a very imposing figure and a great intellect--came to Stanford to visit Mel Cohn, one of his postdoc students. As I mentioned, three of the key people who came to the department were trained at the Pasteur Institute for their postdoctoral work: Mel Cohn, Hogness, and Kaiser. So we were sort of an outpost or a remote colony in St. Louis of the Pasteur Institute.

In 1956, it was apparent that we needed all four building blocks to get the DNA chain to progress. I would have had to have been pretty stupid not to realize that this is what an enzyme has to do to make DNA, and we were lucky enough to have stumbled on the enzyme that does it. Monod said, "Arthur, do you appreciate the significance of this enzyme?" His comment is telling; he thought that I lacked appreciation of what that enzyme accomplished, an enzyme unique in enzymology. No other enzyme had ever been described that took its instructions from the substance it was working on. An enzyme converts A to B; it doesn't convert A prime to B prime.

Obtaining Diverse Scientific Expertise

Hughes: What was your strategy when you found that you needed expertise that was not available in the department of microbiology?

Kornberg: We were designated, and accepted the responsibility, to teach what had been bacteriology and immunology, and which I renamed microbiology, to medical students and an occasional graduate student. When some of the older members of the department who had this expertise departed, we were left without the credentials for, the experience of, teaching various aspects of

bacteriology and immunology. So I tried to learn some bacteriology and virology, and we brought in people to the department who would fill those gaps.

Kaiser came because he was a virologist. Now, he wasn't a legitimate medical virologist; he worked with [bacterio]phages, which was really uncommon in any medical microbiology department. Mel Cohn brought in immunology. We shopped for a parasitologist when the old-line person was about to leave. Fortunately, we couldn't get the person that we wanted otherwise the biochemistry department would have been saddled with a parasitologist.

Hughes: You needed a parasitologist to fulfill your teaching obligations?

Kornberg: Yes, exactly.

Hughes: Parasitology doesn't seem to relate to your DNA interests.

Kornberg: The DNA emphasis gradually emerged. The emphasis grew largely around my work, and the natural interest of someone who is doing genetics to appreciate DNA, which was already clearly the genetic material, and to use it that way. Fortunately, the initial appointments to flesh out a proper modern microbiology department included genetics and biochemistry. So we could be transplanted to a new or different discipline called biochemistry. Now, for some of us, biochemistry was reasonably natural. I had learned it; Lehman had a degree that included virology and biochemistry; Paul Berg got his Ph.D. in biochemistry; Mel Cohn I think got his Ph.D. in biochemistry; Hogness also; Kaiser has a Ph.D. in genetics but, as I said earlier, thinks biochemically very comfortably.

III CHAIRMAN, DEPARTMENT OF BIOCHEMISTRY, STANFORD MEDICAL SCHOOL, 1959-1969

Renovation of Stanford Medical School

The University Administration

Kornberg: In 1955 or thereabouts, the president of Stanford, Wallace Sterling, with proper advice and so forth, decided that the medical school should be moved from San Francisco to Palo Alto. Up until that time, just the first year of courses-- biochemistry, anatomy, and a few others--had been taught here on the Stanford campus; the last three years were spent in San Francisco. Several years later Sterling told me people were calling the move "Wally's folly."

We had an impressive administration here at the time. Wallace Sterling had lofty goals and his provost, Fred Terman, was a no-nonsense, uncharismatic, but very effective person. Fred Terman is responsible for Silicon Valley. He and Wally Sterling were a great team; they complemented each other beautifully.

Creation of the Biochemistry Department

Kornberg: Sometime in early 1957 or possibly even 1956 the faculty of this new medical school here in Palo Alto was being assembled. The job of being chairman of the biochemistry department, a department which didn't exist because biochemistry was taught by the chemistry department, was created. But now in the new medical school there would be a proper biochemistry department, and the chairmanship was offered to Ed Tatum who was in the biology department here at Stanford.

It was assumed--this might have to be documented--that the two people, Hubert Loring and Murray Luck, who had been teaching biochemistry in the chemistry department, would then join Tatum. Hubert Loring had once been a brilliant young biochemist but I think some of that luster had disappeared. Murray Luck was a rather versatile person, did a lot of interesting things, and was working on compounds, called histones, that at that time were considered too difficult or unimportant to study. These now of course are crucial proteins. It was assumed that Hubert Loring and Murray Luck and Tatum would be the nucleus of the new department.

So if it was an embryonic department of biochemistry, it was aborted.

Offer of the Chairmanship, 1957

Kornberg: A very important person was Henry Kaplan, who was radically different from other radiologists in that he was both biochemically oriented and very skilled clinically. We had known each other at the NIH. I don't think we overlapped, but there were a number of personal interactions and friendships. He approached me in the spring of 1957, mentioning the rather amorphous situation in biochemistry and asked whether I would be interested. I said I might be; I'd been in St. Louis four years, a long time for St. Louis. I had come to California several summers to get away from St. Louis.

That was, I think, March or April 1957, and in June, I'd heard nothing further. I had mentioned it to nobody, and it was with some relief that I didn't hear anything further because I was busy with my work and things were going well. Then there was an invitation to come out to look at the job. I might even have said, I'm not interested in looking; are you people serious? They said, Yes, they were very serious.

My group was very close in age and everybody knew what everybody else was doing; it was very much a family affair. I told them in 1957: Don't worry, I'm not going to take this job; I just feel obligated out of friendship to look.

I came out here and, well: Not only do we want you, but you're not being looked at; you're looking at us. What can we do to interest you? And yes, you can bring your whole group to Stanford. You don't have to go through months and years of

search committees and all kinds of bureaucracy. Terman simply said, Okay, bring your group and we'd love to have you.

Hughes: Without examining individual credentials?

Kornberg: Yes, but I think they already knew that this was a stellar group of young people at Washington University. And there would be a new building. Just plan the space. We'll send the architects out to St. Louis; you can design what you want. It was a lovely June day, and they said, "Look, weather has nothing to do with it. Discount that." Very slick salesmanship. I said, "Well the chemistry department isn't that strong." "Well, we're going to replace the chemistry department. We want you on the scene to help us do that." So there was a spirit of rejuvenating both chemistry and biology, and the medical school. I would become one of the senior people.

Recruiting Other Major Scientists

Kornberg: As it turned out, my decision to move here was instrumental in bringing two major stars to Stanford. One was [Joshua] Lederberg, who had been sought after by every other university and had agreed to come because we were moving, and Charles Yanofsky, who was then at Western Reserve.

Hughes: Did they come with the idea of collaborating with you?

Kornberg: Who knows? I think they had confidence in me, yes. There was also the overt movement by the university to support a group like this, and maybe they thought that I would have some influence in its further development. I don't know.

Lederberg really wanted to join my department. I knew him; he's a genius, but he'd be unable to focus and to operate within a small family group like ours, and so, I was instrumental in establishing a department of genetics of which he would be chairman.

Hughes: Which was one of the few departments of genetics in a medical school?

Kornberg: Could be, Sally, I don't know.

Hughes: I found what I think is quite an interesting letter that Lederberg wrote to you in February 1959, when he was already at

Stanford.¹ Stanford apparently approached you first, but Lederberg arrived on the scene before you, which wasn't until that summer. [Pause while Dr. Kornberg reads letter]

Kornberg: I don't know the details. We were coming with a rather large group and there was simply no space here. And I couldn't reasonably take people who were doing really very active and exciting work and ask them to sit here on their hands while Stanford readied space for us. So we were necessarily lame ducks for two years in St. Louis. Lederberg had just his wife and himself and maybe nobody else.

Hughes: One measure of the degree to which Stanford wanted you is that the letter shows that even before you arrived, you were involved in recruitment in several other departments.

Kornberg: Yes, that's probably true.

Hughes: Stanford was creating a new enterprise.²

Kornberg: Yes, that was attractive.

Hughes: But it also gave you opportunities that I presume you wouldn't have had if you had moved to an established school, regardless of who you were.

Kornberg: The most critical thing is how rarely one can create a new department. In most situations, you inherit a lot of people whom you haven't selected. Some of them fare well, others not, and you live with them. So we could introduce a novel way of housekeeping and other things one couldn't impose on an existing department.

Hughes: That must have had a tremendous appeal.

Kornberg: I never thought it through. As I say, these things evolve.

¹ Joshua Lederberg to Arthur Kornberg, February 23, 1959. (Arthur Kornberg papers, Archives and Special Collections, Green Library, Stanford University, SC 369, box 25, folder: 1959. Hereafter, Kornberg papers.)

² In 1959, the clinical programs of the medical school were relocated in Palo Alto where the preclinical sciences had always been taught. For a history of the relocation, see various recollections, including Kornberg's, in a 1984 publication, "Stanford University Medical Center: 25 Years," of the Office of Public Events, Stanford University Medical Center. For a description of the new medical curriculum, see: L.M. Stowe, "The Stanford Plan," Journal of Medical Education, November 1959, 1059-1069.

Reluctance to Establish Joint Appointments

Hughes: I'd like to quote from Lederberg's letter:

[Irving] London says one of his chief motivations [in coming to Stanford] is the chance to develop academic medicine, which includes research training for some of his internists in the basic sciences. I suspect that he is rather concerned that your own perfectionism and aversion from clinical investigation might limit the advantages that such a superb Biochemistry Department might offer as part of the context for his interests. I think he does need assurance as to the extent of your own interest in his program."¹

Kornberg: It is an interesting point, and there is some truth in it. My first paper was on clinical research² and I trained in medicine. I was a happy medical student; I intended to be a practitioner. I was raised in this clinical family and then I rejected it by turning to basic science. [pause]

Clinical medicine to this very day constantly has to make adjustments that I would find distasteful in science. You deal with an individual, uncontrolled; you apply something, and you don't know whether it has been useful or not. I'm very respectful of clinical medicine because I'm a patient; my family members have been patients, and I'm curious about and interested in clinical medicine. But would I take a group of people from the department of medicine and include them as full and active members of the biochemistry department? In some cases, yes, but in a blanket way, no. And so the department of biochemistry here has had the reputation of being very exclusive, elitist, and we have not had the kind of joint appointments that are common in other institutions.

On the other hand, I've been willing to have someone called a professor of biochemistry and pediatrics so that he can

¹ Lederberg to Kornberg, February 23, 1959, Kornberg papers.

² A. Kornberg. Latent liver disease in persons recovered from catarrhal jaundice and in otherwise normal medical students as revealed by the bilirubin excretion test. Journal of Clinical Investigation 1942, 21:299.

maintain his identity with his Ph.D. in biochemistry. But I don't want him as a member of the biochemistry department. So his official attachments are with another department. He can come to our seminars; we're eager to have him use our apparatus.

Stanley Cohen, when he came to Stanford in 1968, used our centrifuges and our apparatus freely; all his early work with plasmids was done with our apparatus.¹ He was really housed in this department. Lederberg says it is about perfectionism; let's say standards--and attitudes and demands we make of ourselves and our students.

When I was a clinician, the patient was paramount; that eclipsed any other consideration I had. It's not like a culture of E. coli; you throw it out if it doesn't work. So doing clinical medicine and doing research are really contradictory. And it is very rare--there are exceptions--that someone can do both well. It's extraordinarily difficult.

I knew Irv London very well at the time. Could we have reached a modus vivendi in which I could keep him and his people happy and maintain our scientific standards? I don't know; perhaps we could have.

Hughes: You don't remember compromising.

Kornberg: I'm saying we never compromised by offering joint appointments.

Hughes: Was that what Lederberg was asking?

Kornberg: I don't know. London, who pictured himself as a biochemist and did some biochemistry, might have wanted some privileges or appointments or whatnot that I might have been reluctant to give. I don't know. But I've had the reputation of being less tolerant.

Relations with Clinical Scientists

Kornberg: Let me say this: my colleagues in the department, all of whom until recently are Ph.D.s, suffer from an inferiority complex because of not having any medical training. They assume when

¹ An oral history is in progress with Stanley N. Cohen, eventually to be available for research at Stanford and UC Berkeley.

you get a medical degree that you acquire a capacity that they simply couldn't get in a Ph.D. program. So, data on animals are more important than on bacteria; data on humans more important than on dogs. There's an exaggeration of the importance of clinical medicine, I think.

I haven't suffered from that belief. When my clinical colleagues on the executive committee or elsewhere tell me this or that is so, I can say, "How do you know it's so?" Whereas my colleagues might be reluctant to challenge a professor of surgery or pediatrics or medicine. I can say the emperor has no clothes. Prove to me he has. Whereas someone with a Ph.D. might think, Maybe he knows what he's talking about.

I think that's an advantage. But it hasn't endeared me to my clinical colleagues. It has given people the impression that I am anti-medicine, anti-clinical science. I don't think that's fair. The clinical science building was built largely through my efforts and those of a group including Lederberg and [Norman] Kretchmer, and a few others'. The dean, Robert Alway, was exhausted. The clinical departments had no research space. We worked evenings, week in, week out to get together the resources to build that building. I was never invited to the dedication of the building. Well, those things happen.

Hughes: You describe a self-sufficient group. Some of it comes, I presume, from the nature of the research itself.

Kornberg: You are very perceptive, Sally; that is so.

Hughes: But it also comes from other factors, which you've been outlining. [telephone interruption]

Hughes: I'm saying that the department has an internal cohesion, but there also seems to be an external exclusion which was thought through.

Kornberg: I think you're right.

Hughes: What about the history of free-standing biochemistry departments?

Kornberg: That was well established.

Hughes: So it was an anomalous situation to have biochemistry within the Department of Chemistry?

Kornberg: I don't know. Where the campuses were split, that might have been the mechanism in those instances. There were quite a few

institutions where the hospital and the medical or clinical group was in one place and the undergraduate in another.

Hughes: Berkeley would be another example.

Kornberg: The Department of Biochemistry at UCSF really was not distinguished and sort of struggling for a long time.

Financial Aspects

Hughes: Did you consider what the neighboring institutions would have to offer?

Kornberg: Not really. Decisions like this are so emotional. With me they are, and with many others. I didn't calculate all the aspects: financial--it didn't matter, even though it was favorable.

My move from NIH to Washington University was unfavorable. I was very naive about that. I never bargained for salary and retirement and moving expenses. I'm not boasting but that is the truth. With my department I've never discussed salary. Isn't that interesting? No one has asked me for an increase in salary.

Hughes: Ever?

Kornberg: Ever. I always felt that I should get the highest salary that was possible within the framework of the institution. In fact, when I invited Esther Sherberg, a secretary at Washington University in St. Louis, to come to Stanford and be our departmental secretary in 1959, she asked for a certain salary and I submitted that and they said: "Well, you can't have that because the president doesn't pay his secretary that much." And I said, "Well, you ought to increase her salary."
[laughter]

Hughes: And what happened?

Kornberg: She got the salary.

[telephone interruption]

Kornberg: Henry Kaplan was still in San Francisco because the medical school hadn't moved. He was influential not only in clinical

and scientific circles but also was recognized as a major figure in the medical school and the university.

Then another figure: Avram Goldstein. He was head of pharmacology, very astute, and had been instrumental in unseating the previous dean, Windsor Cutting. So there was a new dean now; his name was Robert Alway, head of pediatrics.¹ He was one of the people that I had to deal with when I came out for the interviews, and I liked him very much. It was evident that there would be a very supportive, congenial group, and many appointments were yet to be made.

The fact that Lederberg would join the faculty gave Stanford instant visibility, even more so when I got the Nobel Prize a few months after I arrived [1959]. [laughter] Terman, I was told in talking to groups around the country, boasted of this coup in which he had captured a whole department and now with its increasing celebrity was something in which the university took great pride.

Tensions

Kornberg: It had a downside, because in moving from San Francisco to Palo Alto, some of the fine clinicians chose not to move their practice, and the clinicians in Palo Alto felt very threatened. For many years, even to this day, Stanford was and is seen as a medical school of scientific eminence and clinical inadequacy. I'm sure that's exaggerated on both sides. So there was some resentment then I'm sure and has been to this day.

Hughes: In the discussions that must have gone on, was there talk about the new medical curriculum?

Kornberg: Yes, everything would be new. There was going to be a new medical curriculum, not so much by my doing; I neither encouraged it or acquiesced to it. But Goldstein and other young Turks here were pushing it.

Hughes: And Alway.

¹ For more on Alway, see: The Alway Years, 1957-1964, Stanford University School of Medicine, (brochure, n.d.). The brochure, prepared for Alway's retirement from the deanship and hence presumably written circa 1964, traces accomplishments in the preclinical and clinical sciences under Alway's deanship.

Kornberg: Yes. Always was supportive--a very decent man, who then became the victim of impatience and attacks by Kaplan and Goldstein.

Hughes: Why?

Kornberg: I don't know. At Washington University where I was a junior person on the executive committee, the meetings were very orderly, maybe even perfunctory, and the decorum was intact. Here, everyone was squabbling and calling each other names. I couldn't believe it! Poor Alway was actually taken ill as a result of all this and was exhausted after a couple of years.

The estimates for the cost of this medical center were wildly inadequate. Had the real costs been known, it never would have been built. The medical center went into a partnership with Palo Alto which in significant ways limited the autonomy that the medical school would have, having to share authority with physicians in Palo Alto.

Hughes: Was the partnership agreed to largely because of the financial advantages?

Kornberg: I think so. Or maybe there were some diplomatic reasons. Whatever it was, it complicated matters here for a long time.

The New Department of Biochemistry

Choosing Faculty Members

Kornberg: When I decided to move, I invited some people whose names I've mentioned, and disinvited others. Bob DeMars was still in the army, and I didn't invite him to come to Stanford because he was a little bit of a maverick and I had Dale Kaiser. I thought in a small department there wasn't room for an additional appointment in the area of virology.

Hughes: Their science was similar, DeMars' and Kaiser's?

Kornberg: Reasonably so. Science, if it is good, keeps diverging and changing within a few years. I felt we needed a physical chemist in the biochemistry department. Peter Geiduschek, whom I mentioned earlier, had turned us down. Buzz [Robert] Baldwin, identified as a young man of great promise and already considerable achievement, was at Wisconsin. He had been a

Rhodes scholar and gotten a degree at Oxford, and to my surprise was eager to come. He was not yet thirty.

Hughes: Why were you surprised?

Kornberg: Well, because there was no one in the department doing that kind of work. Physical biochemistry was embryonic; it didn't really exist.

Hughes: You mentioned Jerry Hurwitz, whom I believe did not come.

Kornberg: Yes, and that was very traumatic. Jerry and Paul [Berg] grew up together as students. Jerry is more combative and blunt, and was doing very similar things to what Paul and I were doing. It was really sort of a good-natured competition. I had to choose between him and Paul, and I chose Paul. That precipitated a "nervous breakdown", as we called it then. Jerry was just utterly shattered by that, and I've had that on my conscience. But we're very good friends now and have been for many, many years.

Hughes: I know from Love of Enzymes that you were later involved in another competitive situation.¹

Kornberg: Jerry is very competitive. It is characteristic of his work that he does many things at once and wants to push ahead in every one of them. In the case that you allude to, he barged into an area that I was already developing, and I felt that was inappropriate. I wouldn't have done that. If there's an area that intersects with yours and further progress requires that you move into that area, okay. But if you see something attractive but it is somewhat tangential and you move into that area--I didn't think that was very tasteful, especially by someone who is a friend and a previous colleague. So there were ruffled feelings for a while, but that's gone.

Hughes: A member of your lab relayed research results to Hurwitz's lab.²

Kornberg: Yes, Bill Wickner kept talking to his sister-in-law Sue Wickner over the phone. But fortunately, with all those brushes, I don't think there is any residual ill feeling. People go their ways.

¹ Enzymes, pp. 235-236.

² Ibid.

If we take the roll, I think we have covered all the people who moved en masse to Stanford. Six are still together forty years later. They have all been invited to take prestigious jobs and have elected not to leave. The impression is that we've remained intact; nobody has left, and that somehow I've been so shrewd and brilliant in choice of people that there have been no defections. I'll have to correct that, because there have been.

Leaving St. Louis

Kornberg: We were going to be lame ducks in St. Louis for two years. That was not good. When we left St. Louis there was a fair amount of ill feeling. At first, there was the pleasure and pride of having a bright young group like ours and suddenly it was gone. And Kornberg took it with him.

In my defense, all the people that came to St. Louis were recruited by me; they didn't come to St. Louis to be part of the university. Secondly, we left the department in far better fiscal shape than when we came. It was now up to date. We left lots of equipment. We left a legacy in science and in teaching that was then taken intact by my successor, Herman Eisen, who became and has remained a very close friend. He later left St. Louis to go to MIT. So when the dust settled, I think there was very little hostility.

In the summer of 1957, I had to tell Carl Cori that I was going to leave. Well, I hated anticipating this moment but it had to be done, the sooner the better. I approach him and sure enough, Gerty Cori, a member of one of the legendary scientist teams in history, was there. I was delighted she was there when I walked into Carl's open office. He said: "Well, what have you decided to do?" And I said, "I've decided I'm going to go to Stanford. "Ach!" It was the only time in our long association that he was irritated, angered. He sputtered and said: "Well, where will you go on vacation?" [laughter] Gerty immediately calmed him down and said, "Carly, we should have gone to Berkeley when we were offered the opportunity."

Hughes: Had you thought through what you wanted to create when you got to St. Louis?

Kornberg: Number one, the teaching of bacteriology and immunology was not comfortable. This was not my center of interest, and the

reception of it in St. Louis was not all that cordial, even after four years.

Hughes: You mean reception by the medical students?

Kornberg: Yes. The faculty tolerated it; I wasn't being applauded for doing anything novel. Although as soon as this became apparent, I was told by the dean that when Cori retired I would become professor of biochemistry. That was very unofficial. So there were efforts to persuade me, and efforts to persuade some of my people, to stay--Berg and Cohn and others.

Hughes: Was Cori going to be retiring within a few years?

Kornberg: Yes. In 1957, he would have been sixty-one. Retirement at sixty-five was pretty mandatory.

It is important to mention that in 1957 the architects came to St. Louis and we laid out the plans, and everybody was now involved in planning to go to Stanford. In the period in which we were examining the blueprints, we determined what we'd need in terms of apparatus and began to make applications for research grants. Especially in the last year, 1958-59, we spent a fair amount of effort on the logistics of this move: how we would move perishable materials, where they would go, the furniture and whatnot.

Melvin Cohn

Kornberg: During that interval, Mel Cohn had a collaborator, Ed Lennox, who had been trained in physics. Ed later went with Mel to the Salk Institute and stayed for many years; he is now a rather prominent entrepreneur in biotech. He and Mel were working intensely on a basic question in immunology: whether one cell could make two different kinds of antibodies. Mel was singularly disinterested and uninvolved in the preparations we were all making to move to Stanford. He was just too busy doing his most important experiment.

When we got to Stanford, there were many things to do of a custodial nature in getting settled. Again Mel was singularly uninterested. [long pause] I think in a way he felt above it all. As the chairman, I laid out the various responsibilities for the people in the group, with a generous amount being taken by myself. On that list were some assignments to Mel, and he said, "You know, I don't want to do that." I said, "Well,

someone's got to do it." He said, "Well, if I have to do all this crap, I'd be chairman." "Well, you're not chairman and this is what you need to do."

Some months later, shortly after the Nobel Prize, our relations still remained cordial. On one occasion, he said, "Arthur, I've had this offer from Harvard." I said, "Well maybe you ought to take it." That was absolutely shattering. And so, when the Salk Institute was being organized and he was one of the organizers of it, he took the Salk Institute position and immediately took a sabbatical. He was bitter and angry and wrote a very nasty letter which I never saw because it was intercepted by Esther Sherberg. She was a very skillful, wise, and also officious. In fact, she signed my name for the Nobel Prize memoir. [laughter] So it's not my signature.

Hughes: How do you feel about that?

Kornberg: Oh, I don't care. Mel was a major defection.

Hughes: What role had you expected him to have in your Stanford group?

Kornberg: Well, by then he was very much involved in immunology. And while immunology was still not very biochemical, one could see that it would become biochemical. So it was very reasonable that he would lecture on hormones, proteins, and immunoglobulins as biochemical entities. I learned secondhand that the immunology department here resented the fact that the biochemistry department was teaching immunoglobulins, but nothing was ever said overtly.

With a catalytic mind and personality, Mel was brilliant and engaging and intellectually involved. He was a very important person in St. Louis and could have been here as well, but there was a certain aloofness and maybe even contempt for some things that were going on that I found incompatible. His leaving was certainly disappointing to Paul Berg, Dave Hogness, and others, although I never heard from them. They may have even tried to persuade him to stay.

So, his departure, and the two others that I mentioned, document the fact that people left the department as well as stayed.

Relations with the Two Biochemists in the Chemistry Department

Hughes: How did you handle the two biochemists, Murray Luck and Hubert Loring, who were in the Department of Chemistry when you arrived at Stanford?

Kornberg: Not well, not well. I'm sorry that I was not more diplomatic. The chemistry department, as it was being reorganized, wanted desperately to unload these two people on the Department of Biochemistry. Before I got here, Terman broached that to me. I said, no. They were so much older than we were and doing research that was different from what we were doing. I couldn't possibly forego two appointments; it was going to be a small department of seven or eight people. Terman agreed.

I could have found ways in which to involve Luck and Loring more than I did, and I'm sorry I didn't. But I was absolutely right in not including them in the department. No question about that.

Hughes: Did they remain in Chemistry?

Kornberg: Yes. The chemists found things for them to do that were maybe even distasteful to them--teaching elementary chemistry or something else. They didn't want to teach biochemistry anymore.

Communal Structure

Hughes: Your plan for the shape of the new department had larger parameters than just simply the science. It was not just a matter of needing certain people to do certain kinds of science; it was also how they were going to mesh productively.

Kornberg: People have said that this group of people was intellectually very outstanding; it did something very unusual. And I think they did. It is not true anymore because for many years now we are not distinguishable from a dozen other departments. But it was crucial for organization of the department, and my being happy in it, to have this be a family rather than a department of the conventional kind. We are communal in our sharing of all resources--money, space, everything else. And that precipitated the departure of two key people.

Hughes: The communal idea evolved over time or did you come with that philosophy?

Kornberg: I didn't shape it as an idea or a pattern; it just evolved. I think this department is unique in that while there is proper accounting and auditing of grants that are obtained by each of us, unlike virtually every other department in the country or the world, there's no space assigned to a specific person. The result is that each lab has associations with students and fellows from three or four different groups.

Students and postdocs who have left have invariably said that this arrangement was one of the most enriching things that they've had in their experience. They learned not only from what their own group was doing--a group is, on the average, ten people--but they interacted with or were aware of what three or four other groups were doing. And it gave them more friends and contacts with more alumni.

When you share space, that means equipment, supplies, caretakers. The bookkeeping of who takes what, uses what, and so on would be impossible. So we share all our resources. Does each faculty member have a secretary? That would be foolish. A secretary can share the work of two of three professors or contribute when someone's ill or on vacation. So we also pool our secretarial staff.

Some reagents are expensive. There is no point in everybody having expensive radioactive reagents, especially early on when we were all doing very similar experiments. So we go back and forth to our refrigerators and share reagents.

We've had a reputation of being well-heeled, but that's not true. I as chairman or my successors would say: there's a moratorium; you can't buy any more equipment, and you have to go slow on supplies until the next funding interval. Someone uses animals which are expensive; someone uses more expensive equipment. It was crucial that those of us who were in positive balance would say, Well, my colleagues are doing work similar to what I'm doing; we're sharing ideas and reagents and results. Okay, so right now I'm being more generous. That attitude has prevailed

Young faculty members who came into the department were immediately full partners in the whole enterprise. They could take as many students and postdocs and reagents as anybody else, even though their funds were grossly inadequate for that. So there was a legacy of that kind of indebtedness and ultimately responsibility and sharing.

Now, things used to be much better because we were a small group confined to a narrow space and knew what everyone else was doing. You could ask, How did that experiment go, and they'd say, It went well, or it didn't. That is not true anymore. The science has gotten so huge and the forces that take people away are so great.

Hughes: That growth occurred before the department moved to the Beckman Center in 1989?

Kornberg: Oh yes. The phenomenon is worldwide. It isn't unique to us. Even people of not great seniority are constantly being asked to give seminars, to join this or that visiting committee or grants committee. That was not true thirty years ago.

Later Changes in Departmental Faculty

Kornberg: Let me finish with two items that I want to be sure we include in the history of the department. In 1963, we had an appointment that we wanted to make and there was someone that we thought was very attractive. We were six or seven at the time, and three of us thought he was someone we wanted, and the other three were uncertain. He turned out later to be an outstanding person, so we would have done very well to get him --but that's beside the point. Even though I had all the authority as chairman and was in the group that wanted him very much, I deferred to those who had some doubts. That's clear evidence of the democratic nature of the most crucial decisions that one can make, appointing people to the department.

Then we identified two young people who were very attractive and we couldn't decide between them, so we got special permission to hire them both. One was Lubert Stryer and the other was George Stark. Lubert Stryer is an eminent person, who has written the most popular textbook of biochemistry; he's a professor in structural biology now. My son Roger was chairman of that department for a number of years; Jim Spudich, a student of mine, was also chairman of that department.

Lubert Stryer was a very ambitious, brilliant, and mercurial person. His work was going exceedingly well. At one point, I didn't allow him to apply for a grant because he didn't have the space with which to use that extra money. He represented the bulk of my worries and time spent in departmental affairs. He was very good, but very restless. At

one point, we were confronted by his demand to have a wing of the department assigned to him for his exclusive use. He said, "If I don't have it, I'm going to leave." I consulted with each of the people in the department. We didn't have a formal meeting. I said, "Lubert, we're not going to change the philosophy of the department, so if you really want to leave to get this kind of authority and freedom, that's your choice." He left for Yale, where he had his own very generous space, but not long after he was fishing for ways to come back. That's another story.

George Stark was a gem and was in the department for twenty years. He also loved London where he'd been on sabbatical visits several times. He had turned fifty, may have had disaffections with something here and felt attractions in London. He enjoyed ten years of research at the ICRF [International Cancer Research Fund] laboratory and living in London. Now he's back as head of the Cleveland Clinic research department. I've always regretted his leaving, both scientifically and personally. I would say George is the only one who left despite our entreaties to have him stay.

Another who defected is Jim Rothman, who is very prominent in science today, rather ego driven and scientifically gifted, truly a robust personality. Someone said to me when we were recruiting him as an assistant professor, "You know, Arthur, he's not in your style." I said, "Yes, but he loves science and he's so good at it. Maybe he'll adapt to our style."

Hughes: You mean the cooperative family style.

Kornberg: Jim always lived beyond his means. He attracted many students and postdocs and expanded his base. Eventually it was clear that even though he knew and we knew that he was living beyond his means year after year, something had to give, and he left for Princeton. He since moved to become the deputy director at Sloan-Kettering. His work is going well, and he is an international figure. So you see, some people have left us.

Hughes: Yes, I see that.

Kornberg: The image people have is that our group in biochemistry has remained intact for forty years. That is largely true. Hogness, Kaiser, Berg, Lehman, Baldwin, myself have remained together for forty years.

Hughes: Does any other group have that record?

Kornberg: I don't know of any other. We are all members of the National Academy of Sciences, and two people have received Nobel Prizes. Paul has been offered the presidency of prestigious institutes, universities, and others have too. People [in the department] have never come to me with competitive offers from elsewhere. I learned about them only later and indirectly.

I gave up the chairmanship in 1969. Even before that, I had shared decision-making about appointments and so forth. Since 1969, I've remained closely involved in the administration of the department. I don't think I've been intrusive. Rather I've kept concerned and aware of the problems. I give advice if asked. Scientists are like everybody else; they have all the common attributes--

Hughes: I hope so...[laughter]

Kornberg: Selfishness, greed, egotism. They do not always have the greatest wisdom as to how to get along. It has been the essence of this department that your self-interest is best served by being generous and thoughtful. Generosity is its own reward.

Hughes: One could argue that with such a stable group there is a lack of innovation because there is not much new blood coming into the department. What are the downsides?

Kornberg: In recent years, we have brought in new people--six in all. They chose our department because they were attracted to its small size, cohesiveness, and the attitudes that I've mentioned. Rapport between the senior and junior people is very good; our relations are most cordial. This is so, even though the seniors are physiologically aberrant in being active beyond their years. The seniors are respected for what they continue to do, and very much admire the work the young people are doing.

One downside is a perception that the department is very old. Would I as a young person go to work with an older person like me? I guess I wouldn't. I'd want to work with a young person. I'd want him to be here nights and weekends, be ambitious, and be around long enough to recommend me and push me.

Interaction Between the Basic and Clinical Sciences at Stanford

Limited Success

Hughes: As I understand it, one of the purposes for moving the medical school to the Palo Alto campus was to encourage interaction between the basic and clinical sciences. What is your opinion of the success of that endeavor?

Kornberg: Not as successful as you might have hoped--anywhere. Clearly, something had to be done if clinical medicine were to make use of advances in science in an optimal way, for teaching and research and eventually practice. That point can be evaluated differently by different people.

It would be hoped that the preclinical and clinical departments would work more closely together. Was it simply fashionable to do so, or are there more substantial reasons?

The Beckman Center for Molecular and Genetic Medicine

Kornberg: We can digress about the Beckman Center. It was clear as time went on that we needed more space and resources for developing areas of preclinical science--developmental biology, molecular physiology, other burgeoning areas of science. So there were very good and strong reasons for requiring additional space resources to expand and strengthen the preclinical sciences. The problem was not land, because Stanford was very rich in that, but money.

I with others approached Arnold Beckman, who, unlike most rich people, was eager to give his money away, but he wanted to do it in a very meaningful way, which he has done to his great credit. I recall an occasion when he was here and being presented with a proposal to build a center that would house these new departments. The dean at the time, who will be nameless, made a rather inadequate, I would say foolish, presentation. I knew Dr. Beckman and told him very seriously what we intended. He said, "Will you be doing anything really new?" I said, "Not in the sense of starting something utterly novel. What we'll do is provide resources for young and older people to be creative and to work at the forefront of genetics and biochemistry and molecular biological sciences." Dr. Beckman listened and was unimpressed.

A couple of years later when Paul Berg took over the leadership of this new project, the three of us--[President Donald] Kennedy, Berg, and myself--went to interview Dr. Beckman in his home near Irvine and instantly got his approval. But the ground had been laid to nucleate the fund that would build this building. It would be called, maybe at that time it was already known as, the Center for Molecular and Genetic Medicine.

Clinicians as Basic Scientists

Kornberg: I pointed out to Beckman that this center would form a very clear bridge between the preclinical and clinical sciences. We'd bring discoveries to the bedside more meaningfully and more quickly than otherwise could be done. "Well, that's a great idea; we should do that," Beckman responded. Has that been done? Not really.

Hughes: Why not?

Kornberg: Well, because it is rare that you can do both. People who look after patients are consumed with that activity, and they should be. You are consumed with the individual, the uniqueness of that illness, the family, and all the other aspects. You develop some very special skills and a certain kind of routine to respond to an illness by naming it and determining what is to be done or what others should do, and go on to the next patient, and so forth. Of course you're carrying on research and you have a lab. You go there occasionally, and you observe what students and technicians are doing; you write grants and appear at meetings and give papers. But at best you're doing some of both and are not competitive with the best clinicians and certainly not with the basic scientists who have made a choice to do research full time.

Let's take Stan Cohen or Hugh McDevitt or any of the other people here who have appointments in both clinical and basic science departments: when their research is going well and is well received, and they have many applications from students and postdocs, and they get grants, they have to leave the clinical departments.

Hughes: Did those two do that?

Kornberg: Oh yes. I mention them; I could name others. There are instances when there has been defection from basic science to

clinical medicine. Those people generally just do clinical medicine. One of my very best postdocs, who had an early impressive career in science, gave it up, disillusioned with certain circumstances, and he simply went into private practice, with no attachment whatever to science research.

It is very tough to do both. The research that is done in clinical departments generally is a little of this and that, rather than focused on one topic. I'm overgeneralizing, but it often happens. So the considerable stimulation of trying to understand illness is difficult to pursue, because you don't have twenty to a hundred examples of exactly the same genetic background that you can then decide to do thus and so with half of them. Clinical research is tough.

Human nutrition will remain a very ambiguous area for a long time. We understand rat nutrition reasonably well, but human nutrition, which is very similar to that of the rat, is beset by so many problems unique to that individual. You're treating an individual; you are not treating a population of rats. So that tells you why it is difficult to form an effective bridge between clinical medicine and basic research.

Now is it of any value to have the preclinical and clinical sciences at one location? Yes, it is of value because people can go back and forth, and I think the transmission of knowledge, concepts, techniques, does occur. And it wouldn't occur if the clinical people were in San Francisco and we were here, except through the literature.

Hughes: Was moving the clinical sciences to Palo Alto supposed to heal the schism with the basic sciences?

Kornberg: I don't know; I was not here at the time. But I can imagine that some might have pointed out the value to the campus, to the biology department, to the chemistry department, of having some of these clinical disciplines within easy reach. It has turned out that the influence of the medical school on a number of departments in humanities and sciences and engineering has been very considerable. Biology here has been enormously enriched by the variety of biological sciences done here of a very high caliber. I'd say more so in the direction of the clinical sciences helping the humanities and basic sciences than the reverse.

Bridging the Basic Sciences

Hughes: We've been talking about the bridge between the basic sciences and the clinical sciences, but there is also a potential bridge between the basic sciences. You write about what you see as the division between biology and chemistry.¹

Kornberg: Chemistry should have been bridged better than it has been, and I've talked about that. It is frustrating that there has been so little acceptance by the classical chemists of biochemistry. [Instead,] it has been: We know it is important, but we would rather others did it; we want to teach true chemistry. Molecules as bizarre as proteins and nucleic acids and phospholipids--now that's religion; don't bother us with that. That attitude still exists, although there are numerous exceptions now, and I'm sure that most people in chemistry would protest that this represents their thinking. So in that sense there has been progress.

The Medical Center as an Intrusion

Kornberg: The invasion of the campus by the medical school has been regarded comparable to that of the Stanford shopping center. Critics said that the medical school was an intrusion; it would bring nothing but noise and grief and drain resources. In practical terms, if you were to go to donors who contribute to Stanford, clearly those projects with a medical implication would have much greater clout than others. To this day, there is an undercurrent that occasionally bubbles up with fear and resentment of the medical school.

The hospital is an enormous operation that dwarfs the budget of the rest of the campus. It is an intrusion, with all of its commercial activities, a cutthroat industry unlike any other departments in the school. The engineering department doesn't do engineering; the law department doesn't do legal work; so the medical school is unique that way, unfortunately.

Hughes: How did the basic sciences that were already in place in Palo Alto feel about the influx of the medical school?

¹ See, for example: "The two cultures: chemistry and biology."
(Draft, courtesy of Dr. Kornberg, of presentation at Harvard University,
May 28, 1991.)

Kornberg: It must have varied. You should talk to Avram Goldstein, who has now retired, but is very knowledgeable and articulate and perhaps has written about it.

The Basic Science Environment, circa 1959

Kornberg: At that time, there was also a new medical curriculum that was to be put in place with the new organization of the medical school.¹ I told you how the chemistry department felt; they would now get rid of the two biochemists who were teaching biochemistry and, with great relief, have two slots available. It was with great despair that they found that they still couldn't dispose of these people.

The biology department might have had a more sanguine view. Yanofsky was a great addition. He came largely because I was coming to Stanford in biochemistry, and so there would be resources and strength in biochemistry which would be very helpful to him. And then others came. You'd find that there was a very healthy respect for biochemistry in the biology department. The most popular course at Stanford is human biology. That course was generated by people in the medical school who then included people from sociology and psychology, as well as biology.

Hughes: In 1959?

Kornberg: The course was introduced maybe ten years later.

Hughes: Was a basic science environment conducive to interdisciplinary exchange one of the reasons you came to Stanford?

Kornberg: You may find it in my correspondence; I don't remember. I know Lederberg had a joint appointment in the Biological Sciences Department in the School of Humanities and Sciences as well as his primary appointment in Genetics in the medical school. I might have toyed with doing that too, but it doesn't work. It is enough to attend the numerous boring faculty meetings in one school. Almost invariably people hue to one department or the other.

¹ See, for example: L. M. Stowe. The Stanford plan: an educational continuum for medicine. Journal of Medical Education, November 1959, 1059-1069.

I mentioned that it was evident to me that the chemistry department here was very weak and disintegrating. The provost, Fred Terman, said it was the intention of the university not to appoint people under the current regime but to bring in a fresh cadre of people, and to appoint a new chairman. And that's what they did. It was obvious that I was concerned and hopeful that there would be good interactions with chemistry.

Kaplan in radiology was interacting with people in physics regarding the accelerator that they had built for radiation therapy. Goldstein, with his excellent memory and intimate involvement in this move and the details of what was expected, could give you more information.

Later Efforts to Strengthen Basic Science at Stanford

- Hughes: Here are your notes for one of several later efforts on your part to strengthen the basic science component of the medical school.¹ [Pause while Kornberg scans document.]
- Kornberg: "Basic science at Stanford is a paper tiger."
- Hughes: Yes, who said that?
- Kornberg: I did. [He continues reading.]
- Hughes: You were asking for greater integration of biochemistry--
- Kornberg: Oh, it was clear [clearly needed] with chemistry; it was clear with biology. Those facts are there.
- Hughes: You spoke of the drift to the clinical sciences, presumably to the disfavor of the basic sciences.
- Kornberg: The clinical sciences proliferated, with all their specialties. They complained that too much money and attention was given to basic science, which did have much greater celebrity and visibility in the world. They blamed the basic sciences for their own lack of recognition.

¹ Handwritten notes titled, "Notes for Saturday, March 26, 1977, Meeting with Peter Bing, Bill Miller, Clayton Rich, Bob L[ehman], Paul B[erg], Dale K[aiser], Dave H[ogness]." (Kornberg papers, SC 359, box 5, folder: 1977.)

Hughes: I'm trying to establish how the 1959 plan for the medical school actually played out. One of the strands I'm interested in is biochemistry's interaction with other basic science departments. There are indications that the Department of Genetics--

Joshua Lederberg

Kornberg: Oh, the Department of Genetics was created to give Joshua Lederberg a basis for operations. He is a genius, but he couldn't pay attention for any length of time to deal with things like personnel and management of resources. His research has been characterized as being very inventive, but he didn't go on and perfect it. He saw very early that genetics was chemistry, but he wasn't prepared to change what he was doing. He thought I would do it. I invited him to do things with me, but he didn't have the stomach for it. He got interested in exobiology--space--and had a very early interest in the use of computers to do chemistry. He is involved in any number of public affairs now, such as defense policy.

Hughes: Had you hoped that there would be more scientific interaction between Biochemistry and Genetics?

Kornberg: He wanted to be in the biochemistry department at the time that he came here. I saw that--how should I put it politely?--it wouldn't be a good fit. His activities were so varied, and he was such an important personality, that I didn't think he would fit into this modest family atmosphere. I was right.

He's told me that he would have been happier had he been in the biochemistry department so he would be relieved of all of this nonsense. Yet at executive faculty meetings he was far more attentive to the housekeeping of the medical school, of the university, than I was. It was utterly boring, but he paid attention to it, at least for a brief interval. So yes, Genetics was contiguous with Biochemistry. In fact initially we gave up some of our space so that some of his people could be housed until the new clinical science building was built.

The appointments Josh made were diverse--[Leonard A.] Herzenberg, Luca [Luigi L.] Cavalli[-Sforza], [Ann K.] Ganesan. They were outstanding people but they had very little to do with one another, which in his defense is not atypical of departments. A biochemistry department might have a dozen people, each one specializing in some unique area. You can get

better teaching opportunities because the faculty represents a wide range of areas.

More on the Department of Biochemistry at Stanford

Intellectual Focus on DNA

Kornberg: In contrast, this department was narrowly focused. We didn't do research in carbohydrates, lipids, vitamins, minerals, bioenergetics. Ninety-five percent of what was considered important in a biochemistry text was not pursued in this department. Our focus on nucleic acids and proteins that bound nucleic acids was less than 5 percent of the biochemical text. But my defense was, and still is, that we were approaching this rather limited topic, (which of course then got very fashionable), from the very broad standpoint of genetics, enzymology, and physical chemistry. We had Kaiser, Hogness, Berg, Lehman, myself, and then Baldwin. They talked to each other; they collaborated, and then things gelled around DNA when it got to be so meaningful and fertile for studies.

If there is one thing I could say about the intellectual aspect of this department, it was to bring different disciplines to bear on a narrow area of bioscience. We've been applauded for that. Many people have recognized retrospectively that it was really the only department that was sharply focused on DNA biochemistry. Others were doing it, but they were units within much larger departments. Even though we were a small department, collectively we had the critical mass to do the physical chemistry, the genetics, the enzymology of the nucleic acids. I'd say that was key.

Hughes: So instead of reaching outside the department for expertise--

Kornberg: We were generating it here. There were other people-who did even better DNA chemistry or DNA genetics, but within this department those fields were represented at a very respectable level. I have to admit that the enzymology of DNA was done best here. And when we talk about recombinant DNA and genetic engineering, you've heard it said many times, by others as well as myself, that we provided some of the key reagents that made that technology possible.

Hughes: You have described a very self-contained department.

Kornberg: Elitist.

Hughes: And it was doubtless perceived that way. That perception would not be conducive to interdepartmental interchange.

Kornberg: I think you're right. I think we contributed to that perception.

Joint Appointments

Kornberg: It is common among biochemistry departments in medical schools to have joint appointments with many departments. They may have forty or more. To what extent are these joint appointees active in the department? It varies. Some joint appointees may be included in departmental meetings or retreats or sharing of resources. How big can a family be? How many people can you interact with, understand, be sympathetic to, be helpful to, get help from--six, eight, nine, ten people? If they each speak a different scientific language, it is impossible.

Broadening the Focus on DNA

Hughes: I realize that there was a topical focus in the department on DNA, but as time went on, with recruitment, wasn't there an expansion of focus?

Kornberg: I said earlier that we were accused of being very narrow. Yes, there was a narrowing of interest around DNA and RNA and proteins that interacted with them. My defense against that criticism was that, unlike other departments which handle many different topics, we approach this topic from diverse disciplines, disciplines as diverse as genetics and physical chemistry. So in a sense we broadened our focus.

Buzz [Robert] Baldwin was appointed in the new department of biochemistry at Stanford to provide us with physical biochemistry, which clearly was needed for a proper department. He was a specialist on proteins and how proteins sedimented in centrifuges. When he came to Stanford, he started working on DNA, and he has since gone back to proteins. But it is a measure of how interactive we were that he then applied his skills and experience with physical chemistry to nucleic acids. He made important contributions to the literature and to us.

The DNA Club

Kornberg: We had a DNA club which met in the other building, in my room, a room like this one. Virtually everyone in the department attended the DNA club, and for two reasons: one, it was small, and secondly, almost everybody had an interest in DNA.

Hughes: What was the format?

Kornberg: I don't remember. Also, the whole department met in my living room once a month and filled it with cigarette butts and so forth. [laughter] Those were the good old days when the group was small and speaking one language and infused with the excitement of discovery.

Hughes: Was the meeting unstructured?

Kornberg: No, people presented their work in a regular fashion. The same wasn't true of the DNA club. People tell me things about the conduct of those meetings that now seem foreign: the time of day we met, the format, my behavior, which I think has always been so benign.

Hughes: They don't see it that way?

Kornberg: I don't know; I couldn't speak for others.

The Chairmanship

Hughes: I saw a memo written in 1976 to Dean [Clayton] Rich in which you revived "an old suggestion" for rotating departmental chairmanship in the medical school.¹

Kornberg: When I resigned the chairmanship in 1969, it was quite heretical to propose that there be a regular rotation.

Hughes: Rotation wasn't used at many universities?

Kornberg: Well, we used it. I felt that the chairmanship should not be a "life sentence." The letter was to suggest that it be done more widely, to get some turnover and fresh blood.

¹ Kornberg to Rich, June 15, 1976. (Kornberg papers, SC 359, box 5, folder: 1976.)

Hughes: Did you innovate that idea?

Kornberg: I don't think so. But if there is such a memo then I was proposing it because it was not being done at this school, and still is not done in many places. I think we were probably helpful or even instrumental in this kind of practice. Also the pyramidal structure of the departments was severe at the time. It was rare to have two full professors in one department.

In Physics here, Leonard Schiff, at a very young age, was chairman of the department when some very celebrated senior people were in the department. I don't know much about that history, but it must say that one could have a chairman who is lower in rank than some of the people under his executive authority. That is a whole matter in itself. I never thought about it. Except that, I'll say again, in practice I think the rotating chairmanship was reasonable and very useful as a device to get new leadership.

Hughes: I know from reading your essays that you believe that a scientist's first responsibility is to his science. Wasn't there also the idea that a chairman should want to get back to the bench?

Kornberg: Yes. When I first became chairman of an academic department, it was traditional that there was the secretary and the chief officer of the department, and the chairman had an adjoining office. At Harvard it would be palatial; at Washington University, it was also very large. I changed that immediately. I converted the chairman's office to a library. I had my office way down the hall so that I wouldn't be bothered or tempted to get involved in administrative affairs. I had a very small office as part of the lab, with a partition on one side.

Hughes: I would think that in establishing a new department at Stanford, you would have needed to spend a lot of time on administration.

Kornberg: Not really. Again, I placed my office adjacent to my lab and remote from the executive offices. No, I have rather different and I would say heretical views about administration and teaching. So much time is spent on administration that is self generated. For a large fraction of the ten years I was chairman here, one individual consumed 90 percent of my administrative time. Despite the nuisance created, I didn't spend more than 10 percent of my time on departmental affairs. Part of the reason is, I asked everyone else to do various

things, so that I was not the custodian of all the physical and functional attributes of the department.

Hughes: I saw one of those schema outlining specific responsibilities for departmental faculty members.¹ Did you begin that system at the start of your chairmanship?

Kornberg: I don't remember. But people felt that they shared and had a responsibility for the operations of the department. In 1963, when we had a vacancy we needed to fill, we couldn't agree. I actually felt quite comfortable with the choice that I would have made, but it was then not a vote as much as my sense of who felt strongly and who much less so, and then we went on and chose two young people.

Hughes: Was 1963 the year when you began to consider new faculty appointments to be a joint decision?

Kornberg: I'm not sure. I made the decision of who would come to Stanford and who would not. I don't know how much I agonized over it, and I think I've told you there were some serious consequences. Looking back, it was largely a good set of choices.

When we were choosing a physical chemist, we interviewed at least two people, and there was a consensus about Buzz Baldwin, the person we chose. It didn't come up again for three or four years, and then it was implicit that we would arrive at some consensus. It was quite natural too that Paul Berg would succeed me as chairman because he is an interactive person, a boy scout in attitude. He is very generous with his time and concern, bright and accomplished, and he carried on what I had been doing. I didn't feel as though I was no longer chairman. He made some innovations, and that was great. He could have made them without being chairman.

The chairman does have authority and in many instances, in this school and elsewhere, exercises that authority. Even at Berkeley, the chairman can do things without the approval of the department, or sensing that there was a clear majority.

Hughes: Why do you say "even" at Berkeley?

Kornberg: I think Berkeley has an eminent faculty in biochemistry. There are a dozen professors, and they are all very distinguished. I

¹ Departmental Responsibilities, 1975-76. (Kornberg papers, SC 359, box 5, folder: 1974-75.)

am saying that even with a faculty of that size and eminence, the chairman still exercises authority.

More on the Department's Distinctive Operational System

Kornberg: We've discussed the distinctive intellectual features of the department; its operation was even more radical in distinguishing it from other departments within the school or elsewhere. There may be some other examples, but I haven't heard of them: a communal operation, sharing space, resources, responsibilities, and money.

Hughes: You talked about this in the first interview.

Kornberg: I may also have said: the reason people resisted the temptation to go elsewhere to more prestigious, lucrative positions, was that they were comfortable with this system. In essence, it demands that you understand your self-interest to be dictated in the very long term by being generous. It is a human trait, with the exception of a few saints, to believe that you are giving more than you are getting.

Occasionally, we got close to running out of money, so there would be a moratorium on ordering, which was an inconvenience to everybody, particularly those who felt that their budgets were more than adequate. They thought that others in the department were not getting enough grants or spending too much. But strangely enough, everyone felt that way. [laughter] I would go to people that I knew were underfunded or overspending and I'd be told, "I've got enough grants; I'm not overspending."

The reason the department didn't split apart and go to the conventional 'every tub on its bottom' is that we--and I think I clearly was in positive balance--respected what others were doing, even if they were overspending or underfunded; and they were doing great work. One could tolerate some eccentricity, or call it even lack of communal concern.

What is unique at the moment and very worrisome is that there are two professors who are at odds with each other. So we are wrestling with that. I should be out of the loop because my emeritus status makes my involvement anomalous. I am so far past the conventional retirement age. I don't want to be meddlesome. I am concerned with the potential for disruption between the younger and older faculty.

Hughes: How do you in general handle interpersonal problems in the department?

Kornberg: This situation is novel. You try to modify people's behavior and to some extent you can, but there are people who are not going to change in any fundamental way. It leads to divorce in marriage, and it leads to disruption of groups like this. So I think you cannot afford to keep a person like that, even one with great talent, without disrupting the department.

Hughes: So you prioritize the group, rather than the individual?

Kornberg: Clearly, I do. I would not want a genius in the department who would not conform in the general and acceptable way to the behavior that we expect of someone in the group. It is as simple as that. There is enough talent, enough ingenuity in the department that we've been able to attract and keep outstanding people for a long time.

When one of these people that I've referred to came to me repeatedly with plans to get more grants, and I had the authority to sign the grant application, I did not sign it. I said, "We don't have the physical resources, and in my judgement, you don't have the capacity to do all these things." Well, he bridled and disagreed and ultimately left. Twenty plus years later, I still think I was right.

Actually, that was a collective decision. Everybody in the department reflected on it, and it was unanimous. So there was no dissension. And it happened again fifteen years later. There was another such personality: outstanding scientific talent, but again, that inability to live within the confines and the restraints of communal living. And it is a restraint for someone who is expansive and has lots of ideas.

Hughes: And he left as well?

Kornberg: Yes. He is very grateful to me for the intellectual discipline that he acquired here, the objective of 'purifying' a system. You try to characterize a component of the system and do it well.

The Biochemistry Curriculum

The Laboratory for Medical Students, 1959-1965

Hughes: I read that the five-year new medical curriculum was actually not new, that the model was the curriculum already established at Western Reserve University.¹ Do you know if Stanford adopted the curriculum lock, stock and barrel?

Kornberg: I don't remember. At that time I probably not only accepted but maybe strongly promoted that curriculum. I have become so disillusioned with curricula. Let me give you one example; I could give you many more. We were practicing this new medical curriculum--I think it was a five-year plan--and I'll describe the biochemistry curriculum. We took our lectures very seriously, to the point where we attended each other's lectures.

We introduced a laboratory, which was not traditional. Instead of teaching the procedures of biochemistry, how to analyze this or that, we did something that I think was utterly novel. We asked the students to design the experiments they wanted to do. There were only ten weeks, divided into two five-week periods. One assignment was to isolate DNA from some novel source and characterize it; a second experiment was to take an enzyme and demonstrate its catalytic function and supply information that was not available in the literature.

Most remarkably, everyone on the faculty was involved in the laboratory, including our postdocs and graduate students, so there was a faculty-medical student ratio of perhaps one-to-two. The students were very responsive; they would come in evenings and weekends. It sounds so free and open; of course we tried to restrain our reagents in a skillful way. The laboratory was exceedingly popular with the students as shown by the fact that with few exceptions it was done with such enthusiasm. The faculty were also very involved and cheerful about it.

I recall clearly that at the beginning of each session I would tell the students that it was a very different kind of laboratory. The purpose was not to teach biochemistry, but rather to teach how information is acquired and evaluated, the

¹ S. Andreopoulos. A novel curriculum at center stage. Stanford University Medical Center: 25 Years, [n.d.], p. IV-V.

meaning of a control, trust in an observation. Some students might even make some very novel observations. As a faculty we put in more time into this laboratory than into our lectures. But we believed that training a physician in acquiring and evaluating data is an important part of that person's education and training.

We had students in those years, 1959 through 1965, who are today very well-known scientists, and they talk about those days in the biochemistry lab. It really was a remarkable lab.

In 1965, there were some departments that were really inadequate, and yet they were giving lecture courses and laboratories, and there were a lot of complaints about them. I was one of the exponents for a change in the curriculum: a free market--the students could choose the courses they wanted. They had to take a certain number of hours of anatomy, or this or that, but otherwise, there was a lot of latitude. Among the choices they could make was not to take the laboratory because it really wasn't essential for passing the national boards in medicine or anything else.

The year the change was made, 1966, all but four out of eighty-six students elected not to take the laboratory. There were three reasons given: first, it was well known that the lab didn't teach them what they needed to know on the exams. Secondly, it had nothing to do with clinical medicine. Finally, skipping the lab made it easier to graduate in four years instead of five, with significant financial and other implications. In as much as we couldn't provide a lab course for four people, we took them into our own labs, where they were given the exposure of a rotating graduate student. The next year there were no applicants--the end of the biochemistry lab.

The Medical Science Training Program

Hughes: Is integration of medical students into the departmental graduate program a different issue?

Kornberg: It is entirely different. I was talking about how to provide a small number of medical students with an intensive and sustained research experience.

We have the MSTP (Medical Science Training Program). The sponsors of the program, the NIH, insisted that the student

complete both the Ph.D. and M.D. programs. I was opposed to that, largely from my own experience. I thought one degree was enough. The opportunity to do creative research in either program mattered most. A graduate student or a medical student could choose a curriculum focused on genetics, chemistry, whatever, and thereby have the opportunity to do something creative in research. But I was overruled; and yet we have had some outstanding MSTP students.

MSTP was very attractive because it provided tuition, a generous stipend, and an opportunity to get both degrees. You also had the insurance that if you didn't succeed in science, you had an M.D. to fall back on. The credentials and prestige of a Ph.D. might also be helpful. There were obvious practical advantages. The MSTP is still going strong.

Hughes: Why did the five-year M.D. program end?

Kornberg: The five-year program required an extra year of schooling, expense and time. With few exceptions, medical students are there to learn a trade or craft or profession. That mentality maintains to this very day. After four years of college and many years of schooling before that, they decide to become doctors. They want to get on with it and learn what a doctor needs to know.

Just this last semester, the medical students in the biochemistry course were unhappy that it was populated by undergraduates. Imagine the indignity of going to medical school and finding that your near neighbors and competitors in exams were juniors and seniors in college! And by virtue of that you were all being taught things that were not as focused and relevant to becoming a doctor.

The Department's Relations with Industry

Industry Relations in Academic Science

Hughes: In the late 1970s, there was a shift in the tradition that commercial ties in academic biology were not respectable. I've seen some traces in your correspondence that the department had links to industry before that time. For example, I saw a

letter from Du Pont, dated the late 1960s, which proposed a financial connection.¹

Kornberg: A fellowship.

Hughes: Do you have comments?

Kornberg: Let me expand upon this point. First of all, chemistry departments traditionally were tightly linked with industry. Their Ph.D. and M.S. graduates invariably went into industry. Very few went into academia. They were producing them by the dozens; there weren't that many academic jobs. Chemistry departments were tightly linked with industry; they consulted with industry. That goes way back. Stanford, when I got here in 1959, had as one of its guidelines that faculty members could spend one day a week outside the university in some other activity. One day a week!

But in biology it was utterly unknown. That's where the revolution was. So I'd be specific that in the late 1970s this became an accepted and even respected kind of association in bioscience. It was completely novel. No one expected the extent of it.

I had avoided consultantships or any dealings with the pharmaceutical industry. I found my occasional consulting visits disillusioning and disappointing with nothing there that I felt attracted to. It wasn't all that lucrative either, so I wasn't tempted by enormous financial fees.

As described in some of my papers, my virginity ended when [Alejandro] Zaffaroni started ALZA [1968]. I liked him so much and he was so inspiring as a colleague that when he started this new venture and asked me to join his advisory board, I was interested and felt flattered. I didn't know that I could contribute much, and I don't think I did. I served on that board for twelve years and I learned a lot about applied science and business--production, chemical trials, regulatory approval, and marketing.

I learned how difficult it is to translate a good discovery to a point where it is a marketable, profitable product. Without that you're out of business. For example, growing polio virus in a kidney cell in a test tube was an important

¹ Burt C. Pratt, Executive Secretary, Committee on Educational Aid, Du Pont, to Kornberg, October 11, 1967. (Kornberg papers, SC 359, box 26, folder: 1967 A-L.)

feat and earned John Enders and colleagues a Nobel prize. But until it was put into children in a reliable, acceptable, marketable form and proved its utility, the job was not finished.

Yet for one of our graduates to enter industry would have been regarded a disaster, comparable perhaps to the marriage of an orthodox Jew to an orthodox Gentile.

Hughes: Why?

Kornberg: It was not acceptable to degrade and prostitute yourself by engaging in activity that was done under such nonscientific, unproductive, intellectual circumstances. The thinking was that people in the pharmaceutical industry, even if they started off bright, became drudges. Their function was to find ways to avoid an existing patent or to get some new patent based on a trivial thing. Occasionally there were genuine discoveries in industry, but they were relatively rare.

Now it is radically different. Biotechnology ventures and pharmaceutical industry are reasonable career alternatives to academia. There are also attractions to enter law, and start a business--what a revolutionary change in attitude!

Genesis of Biochemistry's Industrial Affiliates Program [IAP]

Kornberg: Now, the Industrial Affiliates Program--do you have the date?

Hughes: As far as I can tell from going through your papers, the Biochemistry Industrial Affiliates Program was first considered in 1979. You mention it in this memo.¹

Kornberg: [scans memo] Yes, that makes sense because this is the time of the Genentech success; and Biogen and Cetus were also getting into the act. Paul and I and others were being approached to start a venture. Having been the source of the knowledge and people doing recombinant DNA work, it was quite natural that

¹ Memo, Kornberg to Dale Kaiser, September 9, 1979. (Kornberg papers, SC 359, box 5, folder: 1979.) An "Industrial Associates Program" is one of several ideas Dr. Kornberg offers as strategies for future funding of the department. The memo is also instructive regarding departmental organization and financial strains.

the department would be seen as an attractive place for a pharmaceutical company or biotech venture to get access to recruit these people and be introduced to the new knowledge that was still unpublished.

Hughes: Who originated the idea of an industrial affiliates program?

Kornberg: I don't know. I'm amazed that I would write this lengthy a memo.

Hughes: You mentioned that Paul had already discussed the idea and that if the department was going to launch an industrial affiliates program, it should do so soon because "[w]e're already a little late in getting into this kind of venture and it may soon become too competitive to make it attractive."¹

Kornberg: Talk to Paul about that. It may have been that he initiated the idea. But it was in the air that our advice and services were being sought, and that we were perceived to be at the forefront of this new technology.

Hughes: There is a precedent for an industrial affiliates program right here on campus.

Kornberg: Oh yes.

The Chemistry Department's Industrial Affiliates Program

Hughes: The chemistry department had an industrial affiliates program in 1970, perhaps earlier.²

Kornberg: Oh yes. It goes back maybe a century that chemists trained their students for industry. But that was not true for biologists. The chemical industry is huge, and it relied on the chemistry departments for its personnel. I would guess that 80 percent of chemistry graduates, even from elite institutions, went into industry, whereas less than 5 percent of biology graduates did so. And engineering, of course, was very intimately allied with industry. Silicon Valley was started by engineering graduates from Stanford.

¹ Ibid.

² Carl Djerassi to Kornberg, July 29, 1970. (Kornberg papers, SC 359, box 27, folder: 1970(A-E).)

Hughes: I have here a letter from Carl Djerassi to you dated July 1970 in which he mentions the department's industrial affiliates program.¹ Was your program modeled after the chemistry department's?

Kornberg: [looks at memo] Well, you are finding more information here than I remember. Archives do make up for bad memories.

Hughes: You're not expected to remember a letter from 1970.

Kornberg: That is fortunate, isn't it? Well, Gobind Khorana happens to have total recall. He not only remembers a paper in detail, but he knows the page of the journal.

Hughes: He has a photographic memory?

Kornberg: Well, it is more than that because he understands what he has read.

At one time I had a good photographic memory because I was under great constraint when I was in college, competing with top students and not having much time--I worked every evening. Before an exam, I almost mentally photographed page after page including footnotes. And that was necessary to compete in City College [of New York].

Hughes: And you could call it forth?

Kornberg: Including poetry that I memorized and knew exactly where it stood on the page. But the half life of that was very brief. Khorana remembers these things for countless years.

Biochemistry's Industry Affiliates Program

Hughes: Do you want to comment on the success or otherwise of Biochemistry's Industrial Affiliates Program?

Kornberg: It was very successful for a while and it is floundering near extinction now. The reasons are several, but largely because we don't have a unique product to offer, and we don't have any super salesmen for what we've got.

¹ Ibid.

Also, our industrial affiliates have become so huge and bureaucratic that when we try to provide them with some perk or privilege--attending our retreats, or presenting some of their work, or meeting with them--our invitation doesn't reach the right people in time for them to participate.

We still have a top flight group of students and postdocs, and industry needs to recruit talent all the time. And our retreats are good scientific meetings and interesting information is presented in a very nice atmosphere. People who might want to attend from Bristol-Myers or Monsanto never see these notices in time to attend because of the time required for notices to filter through their bureaucracy. They are lost on some manager's desk. That's part of the problem.

The main problem, however, is that we don't have an attractive and unique product to sell, and we don't have the salesmen to do it. Some of us were eager salesmen; we'd give seminars at these companies; we'd know the people involved and have some personal interaction.

Hughes: Were you one of those people?

Kornberg: Oh, sure.

Hughes: I know of your association with ALZA and DNAX...

Kornberg: Bristol-Myers, Monsanto, Abbott, and some others. There were several of us who really went out of our way to do this.

Hughes: What was your prime motive?

Kornberg: I think that it had several advantages. It gave us money that was not earmarked; it was money which we then could use for a rainy day. There were threats, some which would have interrupted our graduate program. We could provide stipends to foreign students that weren't otherwise available; we could provide increments to salaries when they were necessary; we could conduct retreats and other activities that might not be appropriate to assign to an NIH grant.

We built up a kitty that was close to a million dollars. Then our chairman was so non-combative that he let the dean consume it. The administration was pressed for money, so they weren't going to give us any to run the department because we had this extra money. Intolerable; I never would have allowed that. It was just not fair.

The affiliates program represented a very good quid pro quo in that we provided access to students and postdocs who were increasingly available to take jobs in industry. They in turn could meet these people in a very nice setting to persuade them or inform them of the virtues of jobs in industry. Early on, representatives from competitive companies had a playing field in which they could interact, and there were some collaborative projects between companies which were generated in this atmosphere.

Finally, I think the program had an educational advantage. We were giving information that would be useful in developing products, and in turn we got some sense of where things were moving in the biotechnology field. It was very useful.

Current Attitudes About Industrial Affiliations

Hughes: What were some of the factors that turned attitudes around about students and faculty having industrial affiliations?

Kornberg: The factors were: when jobs got tighter in academia after the explosive growth in the fifties and sixties, there was a big lag in which all of the full-time equivalent positions were filled. Industry provided another source of jobs.

Secondly, many of the biotech ventures were attractive scientifically, and they in turn influenced the pharmaceutical companies which became increasingly supportive of good science. So the jobs were more numerous and the opportunities to do science were better. They were lucrative. You got a better salary; you got a piece of the company, and people became rich rather quickly. It was also perceived to be the wave of the future. And some people were genuinely interested in applications of knowledge beyond what would be possible in an academic environment. Students saw their faculty involved in some of these ventures and heard how their experiences were worthwhile and intellectually enriching.

The revolution in which biologists became entrepreneurs is as drastic as any other thing that has happened in postwar science. But, to an excess. Discoveries are commonly made that twenty years ago would have been pursued in greater depth in terms of their chemical basis and biological significance to other species, which now become part of a new business. The discovery is immediately translated into a new venture to produce a product that will make money.

Hughes: And what are the effects--

Kornberg: The effects are disastrous. Science isn't being pursued to a depth and a breadth that enriches our knowledge. Discoveries should be developed, but not to the exclusion of the extension of basic knowledge. Then again, the illusion is generally created that these kinds of ventures are not only desirable but imperative, so that the university will make money from its share in the invention; that the scientific fraternity will be seen as part of the mainstream of American life and capitalism; that the country will get rich from the economic advantage of application and discovery; and that industry of this kind can replace the tax dollars that are now being spent to support federal grants. It is like cutting down a forest for the immediate use of the lumber, without having any concern about replacing it. It is very spendthrift and foolish.

Proposing a Scientists' Lobby

Hughes: Do you see ways of halting these trends?

Kornberg: Yes, I'm very much involved in that today. In brief, I'm proposing a lobby of scientists of a magnitude that has not been envisioned, which will then have some voice in Washington. This is a lobby in the best sense of the term; it will inform Congress of the value of biomedical discoveries. That information will then be transferred to every community, where scientists will be available to meet with lay groups and explain why work on, lets say, the pathway of making building blocks of DNA will lead to better drugs and better devices.

One aim will be to dispel the illusion that basic research of any quantity and quality will be done in other than an academic setting. Ninety-five percent of the information that is going to be used in a fundamental way is not obtained in an industrial setting.

Let me make it clear that all of the biotechnology that we have been talking about was done in laboratories that were built and supported by the NIH. It was not done in any commercial laboratory. All the ventures, people and ideas, came from these academic groups. That is still largely true.

Hughes: If the money and the technology to do the science are now more heavily concentrated in industry, aren't young bright minds going to move from academia into industry?

Kornberg: Yes, especially if they observe that grants from the NIH are so difficult to get that established investigators--their research advisors, their role models--can't get grants and quit.

Hughes: That is happening.

Kornberg: It is happening. Or, almost as bad, that the research projects now being proposed for funding are safe, not courageous. In fact, the best projects are those that are already underway, that is, best from the standpoint of getting funded.

More on the Department's Program

Kornberg: When did we start our industrial affiliates program?

Hughes: Nineteen eighty.

Kornberg: By that time, this department had been so innovative in recombinant DNA that pharmaceutical companies were beginning to be interested in it. The department was a very special place of attraction so that we could select a limited number of companies that we would accept as participants in this program. Now everyone is scrounging to find some company to be affiliated with.

It was not only the unrestricted money that the companies would provide; we felt that we would learn something from these biotechnology efforts, and that our students and postdocs might become interested in those opportunities. And that is of course what has happened. But in 1968 when I joined the ALZA board of advisors, it was the first time that I felt I could in good conscience and comfortably be affiliated with a commercial enterprise.

Hughes: As I said, it really took off in 1980, but there was discussion, not surprisingly, in 1979. The first seminar, at Asilomar, was not until early 1981, but companies became affiliated with the department in 1980.¹ What was the impetus for considering such a program?

¹ By July 1980, fifteen companies were reported to be members of the department's Industrial Affiliates Program. (Minutes, Faculty Meeting, July 8 [1980]. (Kornberg papers, SC 359, box 5, folder: 1980.)

Kornberg: I'm going to guess that we were a resource that was relatively unique. As you saw in that letter to Bert Zerner, we did have a focus and an expertise here in recombinant DNA technology and its applications. And so we had a product to sell. There may also have been overtures from various pharmaceutical groups.

What was attractive is that we would get maybe ten thousand dollars a year from each of a dozen affiliates, and that as a budgetary component that was not allocated--had no strings attached--was very attractive in management of the department. As examples, we could supplement salaries of graduate students and postdocs; we could offer stipends to foreign students and postdocs who otherwise were not eligible for scholarships; we could help in getting new faculty members started and do a variety of things that might have been difficult to do with government grants.

Secondly, we were making a contribution to biotech firms by affording them access to technologies and new developments that were ongoing in the department. At these Asilomar conferences [for our industrial affiliates], we could expose our students and postdocs to representatives of the biotech firms or pharmaceutical companies; we were interested in both. And they in turn could recruit or educate them. It used to be unacceptable that any of our graduates would gain employment with pharmaceutical companies. But by that time, some of that stigma had been reduced. It was seen by both sides as an attractive kind of quid pro quo where we were offering something that was valuable and getting compensated for it financially and academically. I would say with regard to DNAX, we were heavily recruiting our postdocs and excellent academic people.

More on the Chemistry Department's Program

Hughes: In a memo on departmental finances, you wrote in 1979 that the issue of an industrial affiliates program was under discussion in the department, and stated: "I think we should consider this a top priority item and do it soon if we do it at all. We're already a little late in getting into this kind of venture, and it may soon be too competitive to make it attractive."¹ You apparently knew that programs of this nature already existed.

¹ Kornberg memo to Dale Kaiser, September 10, 1979. (Kornberg papers, SC 359, box 5, folder: 1979.)

- Kornberg: Well, in the chemistry department they had been doing it for many years. There were very few departments like ours that had such a strong focus on recombinant DNA, but there were others that were getting into the act. I can't think specifically which they were.
- Hughes: Biological sciences departments as a rule did not have industrial affiliations.
- Kornberg: That's true. Even if I sensed we might be a little late, we were certainly among the very first in biology. Then others began to copy our moves in this direction.
- Hughes: You're quite right that the Department of Chemistry here had a program, and I can't tell you exactly when it began. But I know it was at least as old as 1970, because in 1970, Djerassi wrote to you, inviting you to be a speaker in the program.¹ [tape interruption].
- Kornberg: Djerassi might have been the architect of that because he had such intimate connections with industry. But, as I've mentioned, chemistry in general was very tightly linked with industry, and some of the most illustrious academic figures in chemistry were known to have very strong industrial ties.
- Hughes: So there was no stigma in chemistry.
- Kornberg: Not at all.

Current Status of Biochemistry's IAP

- Hughes: Did you see any disadvantages to the Industrial Affiliates Program?
- Kornberg: It has been a concern of late because the program has dwindled and is almost moribund. Were we spending a lot of energy chasing a buck? If we expended a similar amount of energy getting another grant from the NIH, we'd be better off. Also it was evident that in the 1990s we were not offering a unique product. Companies were dropping out and it was difficult to recruit new ones. So, somewhere along the line, we wondered whether it was a good business to be promoting.

¹ Carl Djerassi to Kornberg, July 29, 1970. (Kornberg papers, SC 359, box 27, folder: 1970 A-E.)

- Hughes: Since most pharmaceutical houses did not immediately jump onto the biotechnology bandwagon, did they look upon a program such as this as an excuse to be in touch with this technology, but without having to make a big investment?
- Kornberg: Well, that is some of it. The program has become less attractive to companies for several reasons. One, they already have in-house much of what we were offering them.
- Hughes: But they didn't in 1980, did they?
- Kornberg: Not in 1980.
- Hughes: I'm asking about 1980.
- Kornberg: Yes, I think that was the attraction; that we could expose them to this new technology. We also offered to come and give a seminar once a year without expense to them. But you know they were such large bureaucracies that the source of the money or the contact was remote from the people who would make use of it. So within a company like Bristol-Myers Squibb, one part of the company never knew that they were affiliates of the Stanford biochemistry program. And when invitations went out to come to the Asilomar meeting, they often didn't reach the people who might have wanted to come. And that's partly our fault because we didn't have an organized, aggressive person or group within the department to correct for this lack of communication. I think the program has had its day.
- Hughes: At one point you actually had a non-faculty member in charge.
- Kornberg: That was someone [Elizabeth Kirk-Fulton] in the department office, and they were not fully directed to that. It was one of their duties in addition to secretarial or some other duties.
- Hughes: That implies how the department weighted the importance of this program.
- Kornberg: We were very eager to maintain and extend that program, and I think it was successful for at least a dozen years. And maybe that is the lifetime of any enterprise like that.

It was disillusioning too with Genentech. After all, Genentech existed because of the technologies we'd introduced; some of their scientists came from Stanford; and after one year they opted out of the affiliates program. At that time, it was ten or twelve thousand dollars a year; it was a trivial amount even for companies that weren't making any profit. Some of the

biotech ventures were involved briefly and had very tight budgets.

The large companies used their research budget, rather than some other budget, to pay for the affiliation, and so corporate research people there would say, well, this affiliation is worth half a postdoc or half an assistant. Surprising how narrowly some of these multi-billion dollar companies could look upon collaborative arrangements that could be helpful.

Smith Kline & French¹

- Hughes: I saw some minutes of a faculty meeting in late 1981 about Smith Kline.² Apparently there was consideration of the company underwriting a postdoctoral training program in the department.
- Kornberg: Smith Kline at that time had a middle manager involved in university relations--wish I could remember his name; a very nice person--and I think they did underwrite a fellowship for a few years. [pause]
- Hughes: George Poste.
- Kornberg: Yes, Poste was in charge. [pause while looking over minutes] Who wrote up these minutes?
- Hughes: It varied from meeting to meeting.
- Kornberg: I don't remember exactly what became of this.

¹ Now, SmithKline Beecham.

² Minutes of Faculty Meeting, November 16, 1981. (Kornberg papers, SC 359, box 5, folder: 1981.)

Potential Conflicts of Interest

Hughes: I'm interested in the basis for one opposing view, which came from Brutlag.¹ Apparently the faculty was concerned about a departmental relationship with a specific company.

Kornberg: Yes, that is always a very serious matter. We were steadfast in not wanting to have an exclusive relationship with one company. Scripps has been very successful--Richard Lerner, the director, has been the architect--in such exclusive arrangements.

Hughes: Brutlag's point of opposition was not so much the exclusivity of a relationship with Smith Kline, but rather that having a relationship with Smith Kline might interfere with his relationships with other corporations. I thought that was an interesting twist. [laughs]

Kornberg: That of course affects people who already have an industrial relationship.

At an early stage, I was approached by another biotech venture, and I consulted with Schering-Plough, which a few years earlier had bought DNAX, and they felt very strongly that I shouldn't be involved with another venture. Later on, that changed; there were pros and cons. One is a direct conflict of interest--and that was not true in this case--where you have a competing firm and then unconsciously divulge information to a competitor. Schering Plough's argument was more that I was a commodity that would be reduced by being shared with other companies.

That has changed now; it can be seen as an advantage that in knowing and being involved with another company or venture I could catalyze contacts between them and be more broadly informed so that I could be a better consultant.

Kornberg's Relationships with Industry

Kornberg: Over the years I've been involved with a half-dozen different companies. On the whole, it was worthwhile. The financial

¹ Douglas Brutlag memo to Dale Kaiser, November 30, 1981. (Kornberg papers, SC 359, box 5, folder: 1981.)

rewards have been significant; they've not been overwhelming. I've enjoyed meeting people from another walk of life. These are lawyers, accountants, investment people, marketing people, and I do appreciate the problems they have to solve; they are genuine problems; they are not fictitious in any way. And I appreciate the expertise they bring to bear and their outlook on life. Maybe I am lucky or overly impressionable, but I found them attractive people for the most part.

Hughes: Are you a bit surprised?

Kornberg: I am surprised, yes.

Hughes: Did these connections with industry present a new vision in respect to your own science?

Kornberg: Not in respect to science; just to people who create ventures in society. I've not been involved with philanthropies; these are business ventures. On the whole, I found them honorable, bright, and creative people. Their integrity matches anything I encounter in academia. Also, I've dealt with a few patent lawyers, and I like them. I wouldn't want to do what they do, God forbid, but given the society we have and the opportunities for people to do a variety of things, yes, I find them bright and engaging. That's of course the patent attorneys on my side. On the other side, they are just villains. [laughter]

IV RESEARCH PROGRAMS

DNA as the Genetic Material

Hughes: Dr. Kornberg, can you pinpoint when you became aware that DNA was the genetic material?

Kornberg: As I mentioned earlier, I confess to not having as a focus of my attention the chemical basis of heredity. But I was not inattentive to discoveries that were relevant to it. I think I might have appreciated that DNA is the genetic material even earlier than geneticists who were focusing on that question because I was aware of the Avery paper which used deoxyribonuclease to identify the transforming factor as DNA in the Pneumococcus; I trusted that enzyme.

Others for theoretical reasons decided DNA would not be complex enough to carry that much information. The knowledge of DNA chemistry was primitive enough that they couldn't be satisfied and believed that there might be a protein that carried hereditary information. The geneticists, who were in most cases above the "mumbo jumbo" of biochemistry, really didn't care that much. So it was not until a rather inexact and I'm going to say primitive experiment by Hershey, the Hershey-Chase experiment, showed that the genetic information from the bacterial virus resided in its DNA content rather than in its protein coat. Only then, the phage fraternity--because one of the members of that church had done the experiment--decided that, yes, Avery eight years earlier was probably right, the genetic material was DNA.

Then there was great impetus from the Watson-Crick model, that not only reconciled the physical facts about DNA in terms of the double-helical structure but was also the means to understand its replication by base-pairing--copying of each of the parental strands.

Hughes: Was the significance of Avery's experiment generally appreciated before it became clear that DNA was the genetic substance?

Kornberg: Avery--and [Colin M.] MacLeod and [Maclyn] McCarty who were his younger associates--clearly appreciated that, and in his very modest way, Avery understood its implications. As I say, a key element in that proof was that an enzyme had been purified that was specific for degrading DNA. It was not a protease. It destroyed the transforming factor principle, as they called it at that time.

You could argue that the DNA was a scaffold or a protective device that kept the true genetic material, protein, in an active state. Some people did; they actually challenged the assertion that DNA was the genetic material, including Alfred Mirsky, who was a very prominent biologist at the very same institution, the Rockefeller [Institute for Medical Research]. So the assertion was controversial.

DNA also wasn't the center of attention in biochemistry or biology that it later became. I've said several times already that the geneticists at Caltech, who were the outstanding group in 1952, gave it very little attention before the Hershey-Chase experiment. You'd have to do research to find out how widespread was its acceptance or its rejection, but I would say it was not the focus of attention, and it was not widely accepted.

Research on DNA and RNA Polymerase

Hughes: Why did you become interested in the synthesis of DNA?

Kornberg: To repeat, I was interested in how enzymes function, and specifically in how enzymes might lead to the production from simple materials of the building blocks of DNA and RNA. And thereafter, knowing what the building blocks were--namely the nucleotides of a certain structure and composition--I wanted to learn how they might be added to an existing chain of DNA.

Then, as is well known, from the studies we did and later others did, we discovered an enzyme, which we named DNA polymerase, that does more than simply add a building block to a preexisting chain. This enzyme, wherever you find it--and it is found everywhere where DNA is made--takes instructions from preexisting DNA and therefore replicates the genetic material.

It was not lost on me that this enzyme with these very impressive properties of copying a template was of direct importance in the replication process. But I can't say honestly that I sought that enzyme to solve a biological problem.

I do want to emphasize that it has been my conviction, and it's the basis of the books I have written on DNA replication,¹ that you have to know the actors in order to understand the plot. And the actors are the enzymes. They are the mini-chemists, the devices by which a biological phenomenon takes place, whether it is the legendary question of alcohol fermentation--how the juice of a grape generates a fine wine or champagne--that bedeviled people for over a century, or how a firefly comes to luminesce. Applying that same reductive approach to replication and to other phenomena, I believe we can get to the core of biologic questions and phenomena--by finding the actors, and the actors are the enzymes.

So in this case we were rewarded by seeking out an enzyme that does something as simple as adding one building block to an existing chain, and finding that this event required that for building a chain you have all the components that enable the actor, DNA polymerase, to do its job.

Hughes: Am I right that your interest in the synthesis of DNA was not so much because it happened to be the genetic material but because it was a logical extension of your previous work?

Kornberg: That's absolutely true. And I believe I've said so in my book and to you a few times. It's an admission, but yet in being as honest as I can be, it proves my point that a focus on enzymes can lead you to the solution of biologic questions that you don't anticipate. It may take time; it may be roundabout. I'm emphasizing that because this faith--this dogma--is hardly practiced now at all. Apparently there is such an emphasis on genetics to solve problems, and its offshoots in cellular biology, that enzymologists are a highly endangered species. Enzymology is practiced now by chemists who are curious about the intimate catalytic mechanisms in the structures of the enzyme rather than their biologic functions. And because of this division of cultures between biology and chemistry, the enzymology that falls in between is very much neglected.

¹ A. Kornberg, DNA Synthesis. San Francisco: Freeman, 1974. A. Kornberg and T. A. Baker. DNA Replication, 2nd ed., San Francisco: Freeman, 1992.

Joseph Fruton's Reaction to DNA Polymerase

Kornberg: I knew Joseph Fruton at Yale pretty well, and he was my host at Yale in 1958. After I had presented my work, which was by then almost iron clad, he said, "You know, Arthur, I can't believe that an enzyme would take instructions from its template. No enzyme has been known to do that." My response was, "Well, Joe, how else can you interpret these data? What's more, isn't this an unusual situation for which you would need an unusual enzyme to do the biologic job that has to be done?"

Hughes: Why is it unusual?

Kornberg: Well, as I've said, Fruton says an enzyme is designed to do a job and doesn't take instructions from a substrate. So how does the enzyme know to put a T next to an A or a G next to a C? How does it select the A, T, G, and C on instruction from what is in the preexisting DNA? Well, once you accept that, you can imagine how such structures could be oriented on the surface of an enzyme to do that.

Hughes: It was shocking to you, too, wasn't it, when you first discovered it?

Kornberg: Yes. But that was three years earlier. And we had lived with it. And maybe I wasn't as steeped in the history of enzymology as Fruton was. He had written the most authoritative textbook, and was a very estimable scholar of enzymology, biochemistry, and history.

Hughes: But pursuing the research on DNA synthesis as you had, wasn't the conclusion inescapable?

Kornberg: It was inescapable. I'm saying that someone as experienced and erudite as Joe Fruton, two years later couldn't quite accept it; I mean, it went against the grain.

He wrote an autobiography on his eightieth birthday which came out two or three years ago. It was circulated to a limited number of people and he sent me a copy. He asserts in the preface the standards of historical narrative that he follows, and said that he wouldn't do anything as irregular as what Kornberg did in his book, which was to quote somebody without having the exact quotation available. He went back to his notes for that day, and found no notation of his having been engaged in that conversation with me. Number one, does he have in his daily notes a complete transcription of everything that happened that day? Number two, isn't it obvious that

thirty years later when I quote a conversation that I'm not using the text? I'm using it to convey the spirit of the exchange.

Then, I think in a footnote--this is where my memory fails me--he states that the enzyme that I described at the time wasn't the true replicative enzyme. [laughs] Which is utterly ridiculous, because all replicative enzymes have the property that was confounding him. The fact that there are other DNA polymerases which have different functions doesn't alter the fact that they all carry out the very same basic catalytic activity of matching a template with a nucleotide. So he made the ridiculous accusation that I didn't quote him correctly, and then compounded it by still being confused thirty years later about the very nature of DNA polymerase.

E. coli Mutants Without Polymerase

Hughes: The episode reminds me of the controversy about the E. coli mutant that appeared to do without polymerase. Is that pertinent?

Kornberg: Exactly. Nature New Biology¹ went a step beyond that in saying that the mechanisms that we worked out so painstakingly for some fifteen years might not apply to the true replicative enzymes that were operating in this mutant. You know, the pendulum swings. True enough, we thought that this DNA polymerase was adequate and could perform in the cell the replicative functions which we observed in the test tube. And it wasn't until that mutant was discovered that the strong possibility was raised that other DNA polymerases were operative.

About that time, Crick was angered almost to the point of fury that reverse transcriptase, which copies RNA back into DNA, had violated his dogma of DNA to RNA to proteins had been upset, and it was headline news. He was very angry about that. He said that he didn't regard it as contrary to his dogma that nucleic acids might be interconnected, but that nucleic acids did dictate the structure of proteins. That was his dogma.

In 1970, I was sharing an office with Crick in Cambridge, at the time of this vendetta by Nature New Biology against my

¹ Nature New Biology 1971, 229: 65-66; 230: 258; 233: 97-98.

DNA polymerase. He said, "Oh, forget it. It's like trypsin and chymotrypsin; they have essentially the same function but they are designed a little differently. When they find this new polymerase, it will be much like what you've described." And he was absolutely right.

Then a year or two later when reverse transcriptase was discovered, and the excitement was that the Crick dogma had been upset, he was furious [laughter], and wasn't all that impervious to the noise and excitement about his being attacked for his dogma.

Hughes: In the end, did the Nature New Biology editorials provoke a discovery?

Kornberg: I don't know if the editorials did.

Hughes: The thinking that they represented?

Kornberg: Obviously, the Cairns mutant was very provocative because the genetics of E. coli, beyond that mutant, established that there were additional genes that were needed for replication and were numerous enough to imply that they encoded novel factors without which coli couldn't replicate. Among them was one that dictated a new DNA polymerase. There were still others. So it was obvious that we didn't have the whole story, that replication was enzymologically much more complex than this one enzyme could explain.

Also, we hadn't answered several critical questions. We didn't know at that time how a chain got started; we didn't know what the controls were for starting a whole cycle of replication, for starting a chromosome--many questions. In lectures, just to be amusing, I show the picture of the replication fork with its fork covered discretely by a fig leaf. [laughter]

A person I thought was a friend mine, Noboru Sueoka, a pretty knowledgeable person, gave a talk at Stanford on some aspect of replication and started off by saying--with me in the audience and the host--that the replication process is utterly obscure. I was irritated because he could have said, "We've learned a great deal about replication but there is so much more to know." That would have been not only diplomatic, but I think more accurate. The questions about replication are far more numerous than the things we can cite that we know clearly. The machine that does the replicating is awesome. How it is assembled and exactly how it functions are still major questions.

Tom Kornberg's Contributions

Hughes: Do you want to talk about Tom Kornberg's role in working out some of these problems?

Kornberg: Well, it has been recited in my book.

Hughes: You could say how you felt about his work.

Kornberg: It is difficult to relate honestly how my feelings were, unless there is a written record, and I don't have one. It was a very mixed set of emotions. Here is your child who loved the cello, who was devoted to it without any parental pressure, who would spend many hours in the day--four, five, six hours--practicing a few notes to get them right. Tom was very driven and motivated, and gifted enough so that he was accepted by the premier cellist in the country, Leonard Rose, as a student, and at Juilliard [School of Music]. He was doing very well and had the mental stamina to cope with Yo-Yo Ma, who was his classmate.

Then he developed a lesion in his left index finger, which was like a major athlete losing his arm or leg and being unable to function. It was very painful, and he simply couldn't use his finger--very traumatic. It looked like the termination of his musical career at which he had labored more than ten years. And to this day, he is a very fine cellist and loves music. That's one side of it.

The other is that unlike Roger, his older brother, or Ken, his younger brother, Tom was so devoted to music that he hadn't had any lab experience. In the place of music, he was going to try to do what Bob Lehman, Charles Richardson, and others who were very practiced at research on DNA replication and [DNA] polymerase were unable to do. I thought he'd waste his time, get frustrated further. So my advice was, "Tom, these people have tried to find the other enzyme in the Cairns mutant; they haven't been able to do it." So yes, I discouraged him.

Then he went to work in a lab at Columbia where he was also a student, and where Malcolm Gifter gave him lab space and--I don't know the details--modest encouragement. Within weeks, he had manipulated cells and extracts, and demonstrated that, yes, in these mutants there is another activity. Then months later, he found that he could detect still a third activity which proved to be the ultimate polymerase. I know that Jerry Hurwitz, who can be a very accomplished and decent person but can also be carping and critical, ridiculed the data on which

Tom was basing the claim that there was a third polymerase. Tom turned out to be right.

There was an international conference in Switzerland, and Sol Spiegelman, who was a major actor on the scene, very bright and accomplished--I think maybe to show me up--featured Tom's presentation at a major symposium at this international meeting, just a few months after Tom had first entered a lab.

What are my feelings? Certainly pride. And why did Tom do it? I think he did it out of loyalty. He wanted to show that his father, unlike what was being said in lectures and hallways, was not misleading the world as Nature New Biology was claiming, but that there was a likelihood that for some reason in this mutant, my DNA polymerase was being masked or somehow inhibited. Years later it was shown that many mutations of this enzyme were lethal because of its other functions: its capacity to engage in the removal of the primer RNA is essential, also its capacity to fill the gaps created by removing the priming RNA. But clearly the major discovery was that there is another far more complicated DNA polymerase.

Gefter got a prize for that discovery, and didn't deserve it; it was Tom's work, which Gefter then expanded; he was instrumental in the genetics that established that this new polymerase was a truly novel protein encoded by a different gene.

Hughes: Why was your earlier work on polymerase I considered misleading?

Kornberg: Well, for no good reason. There were people who were eager to make news and jump on some Achilles heel of a person or an institution. It is newsworthy that some leading figure or some leading idea is vulnerable or can be discarded. In the current New Yorker, it is [Bruno] Bettelheim, the psychologist, who is being dismembered by biographers. I'm sure that there is a disproportionate eagerness to consume the target.

Severo Ochoa's Research on RNA Polymerase

Kornberg: Let me give you an example: A postdoc in Ochoa's group, Marianne Grunberg-Manago, and Ochoa believed they had discovered RNA polymerase. It was their evidence at the time that led me to abandon early experiments that were leading us to RNA polymerase. That was a classic example of where a

plausible interpretation needn't necessarily be correct. We were misled by that, and it was one of the significant mistakes among others that I've made. Having discovered an enzyme that could make something that resembled RNA, they then concluded that they had discovered the enzyme that made RNA. That was wrong.

It was on the strength of that work that Ochoa got the Nobel Prize. He deserved it amply for many other discoveries that he had made that were germinal and significant, but that wasn't the one. The enzyme later was shown to be a scavenger, an RNA disposal recycling mechanism, that has nothing to do with RNA synthesis.

In fact, Fruton whispered to me at some point before or after 1958, "I think you've got an enzyme that makes DNA, but I don't think Severo has it [RNA polymerase]." And Fruton was right; many of us were convinced of that.

Hughes: But you must have initially thought that Ochoa had found RNA polymerase, otherwise you wouldn't have abandoned your own research.

Kornberg: Yes, I'm saying it was a mistake. But a year later, their work began to be more tenuous, and two years later, even more so, so that people were whispering, "Hey, this enzyme doesn't behave like an RNA polymerase."

But looking back on it, if we had stuck to our guns and pursued the assay we had in hand and had discovered RNA polymerase, that would not have been a trivial discovery. To my great disappointment--I was hurt by it--when Ochoa became aware of the work we were doing on DNA synthesis, he was about to plunge in and work on that as well. I thought that was, to put it mildly, improper, maybe unethical. But in some instances there are people like that who say that this is everybody's territory; why can't I work on it?

Hughes: And indeed he did?

Kornberg: No, he didn't. I think our progress was so rapid and the work went so well that nobody could catch up.

Hughes: Did Ochoa consider taking up research on DNA polymerase after the news that his RNA polymerase was not the right one?

Kornberg: I can't remember.

Kornberg's Research on DNA Synthesis

Hughes: Well, I want to quote you from a 1984 lecture: "My own attempts at synthesizing DNA with enzymes in a test tube were regarded by some as audacious."¹ Why?

Kornberg: Anyone at that time who understood the nature of a substance complicated enough to give genetic information would have been quite awed and discouraged that you could find a purified entity that would do such an unprecedented job. As I've been saying, Fruton, confronted several years later with the evidence, was still finding it hard to swallow. He was certainly in the minority. But remember, he was a thoughtful and accomplished scholar in biochemistry and various aspects of the history of biochemistry. So yes, it was audacious.

I was inspired by something far more trivial, which was the building of a glycogen chain. Not trivial to me--I thought it was magnificent--but something like that is all I'd hoped to accomplish. So even I thought it was audacious. But I never stopped to think that I couldn't try something in my work, and as I said time and again, it worked even beyond my dreams.

Hughes: Was there a certain aura around the nucleic acids?

Kornberg: There was a bad aroma. [laughter] They were messy. Remember that nucleic acids just a few years earlier had been thought to be a monotonous succession of tetranucleotides; a few years earlier, just a little molecule of four nucleotides. And then their polymeric nature was discovered; their complexity; the Chargaff rules; they became more and more complex. How do you isolate a nucleic acid? No one knew how to do that. Proteins were being isolated as homogeneous entities from a morass of proteins, but not nucleic acids. There was no entity that you described with a formula. It was a mess. Serious biochemists weren't working with nucleic acids.

Hughes: Did those obstacles ever give you pause?

Kornberg: Not really. [chuckles] I just didn't know enough to be discouraged. I was not that astute.

¹ A. Kornberg. Understanding life as chemistry. In: Medicine, Science, and Society: Symposium Celebrating the Harvard Medical School Bicentennial, K.J. Isselbacher, ed., N.Y.: John Wiley & Sons, 1984, pp. 7-17.

In 1970-71, three or four years after we'd "created life in the test tube"¹ and had used a homogeneous DNA, the circular DNA of a virus, as our template, we still didn't know how to start a DNA chain. After faltering and frustrating experiments for four or five years, I then learned the importance of one of the Ten Commandments of DNA enzymology. We had certainly observed the commandment: Don't waste clean thinking on dirty enzymes. But not the next commandment: Don't waste clean enzymes on dirty substrates.

I make the point that there was no dirtier substrate than DNA. When you get it out, it is fragmented, frayed, all messed up, because it is a large molecule, and sheared, broken up, and degraded by enzymes. That truth finally dawned on me. It was at that time [1971] I said, "Well, if we want to find out how to start a DNA chain, we'd better work with an intact DNA molecule. And that could be furnished by a virus, a bacteriophage, in which we could actually see that the DNA circle was intact, both chemically and under the microscope.

You are aware of that controversy about accepting our papers on DNA polymerase by JBC [Journal of Biological Chemistry]. Ten different people were involved in an extensive review and initially rejected the paper, because we called it DNA. They were willing for us to call it polydeoxyribonucleotide. According to some of the reviewers, the authorities in the field, DNA implied genetic material, and we hadn't proved that the product of DNA polymerase action was a genetically active, biologically active product. My contention was that I didn't want to diminish the significance of the title by calling it something as nondescript as a polydeoxyribonucleotide, when it was DNA by a definition that had been used by that journal in 98 percent of its papers.

Hughes: So why were they singling out your work?

Kornberg: I think a reluctance to have any implication that we were advanced enough to synthesize "real" DNA.

¹ A phrase used by the media, including Stanford's news bureau. See Stanford's news release on the Kornberg group's synthesis of viral DNA. (Stanford University School of Medicine, News Bureau, December 14, 1967. Kornberg papers, SC 369, box 18, folder: press conference December 14, 1967.)

Synthesis of Viral DNA, 1967

Scientific and Popular Responses

Hughes: Was what you had achieved with the synthesis of a biologically active virus appreciated for what it meant for science?

Kornberg: The popular response to it as I told you was excessive. It was over appreciated in terms of what it actually represented. It was something like Dolly [the cloned sheep]. It was on front pages that we had created life in the test tube, just as it's a front page story in the [San Francisco] Chronicle that an artificial human chromosome had been created. As I mentioned in my book, Max Perutz, the venerable scientist in Cambridge, England, wrote a rather caustic letter to the London Times saying, in effect, "What is all this hoopla about? Kornberg's doing things that were scientifically anticipated. It isn't all that novel."

I think that both responses, awe on the one hand and deprecation on the other, were inadequate or improper. First, the public perception that I'd made a virus, one of these big ugly things more complicated than the bacterium in that it makes you sick--was not a proper understanding of what had been done. And Perutz's appraisal--to pick on him because his criticism was public--was not adequate either, because we did show that we could synthesize an infectious molecule, meaning that it has 5376 nucleotides probably in the correct order. That hadn't been done before. Our enzyme had that much accuracy and fidelity.

Second, we used synthetic nucleotides, proving there were no novel nucleotides in an infectious DNA. That had never been known before. Yes, it is as simple as A's, T's, G's, and C's. And then we pointed out in the paper that this could be used for site-directed mutagenesis, for which a Nobel Prize was given some years later. We could do so by introducing a novel nucleotide that would be the source of a mutation. We pointed out that we could put in analogous nucleotides that were foreign and therefore the source of mutations. That was not fully appreciated.

Hughes: Why wasn't it?

Kornberg: Well, Lobban's work in recombinant DNA didn't get its full or adequate appreciation in 1974.¹ That was seven years later. And frankly, if we thought this ability to cause mutations was important, why didn't we exploit it? The same thing is true of PCR [polymerase chain reaction]. Why did [Kary] Mullis get a Nobel Prize for it fifteen years after all the elements of PCR had been demonstrated? Well, it just wasn't exploited. Why wasn't it exploited?

You could ask that question from now to eternity. Why at a given time were people not as impressed as they might have been? Or why is Jules Verne now venerated for all of the seemingly absurd predictions that later turned out to be genuine? I think it's just a reflection on how inadequate our perceptions are, not of the possibilities, but of the time scale. If we talk about biotechnology and its pros and cons, it is something like [Gordon] Moore's law for transistors and silicon chips: a doubling in capacity every eighteen months. The chips now carry information that was absolutely unanticipated, undreamed of ten years before.

Technology builds on technology; ingenuity then builds on advances and exceeds the time scale. And sometimes it lags far behind. The World's Fair of 1939 made all kinds of predictions of what society would be like. People would be flying around from one place to another like birds. Some things happen; some things don't. Okay?

Hughes: Okay. You mentioned the press response and I know from having looked through your papers that it was tremendous. It seemed to have been covered in virtually every paper of any size in the country.

Kornberg: In the world.

Hughes: How did you feel about that?

Kornberg: Bewildered. The best account was by Alistair Cooke, a television personality with Masterpiece Theater. I've been a great admirer of his since, because I really didn't know much about him before. Bruce Blevin I think was the editor of a major magazine, New Republic or The Nation or something. He was very well known in literary circles. His daughter, Naomi Blevin, is a regular book reviewer for the New Yorker.

¹ Peter Lobban's work is discussed below.

Alistair Cooke was a friend of the Blevins whom I met through my son, Ken, who lived in the same apartment building while he was at Stanford. Cooke was correspondent for the Manchester Guardian and his account of viral DNA synthesis was so sharp and clear that I quoted it in my book. He was also very flattering; that mattered too.

So where does life begin? At what point do we socially accept its sanctity; its inviolability? It is in the succession of molecules that in becoming more and more complicated get to be self sufficient. There is no question that E. coli is living. It has personality; it has locomotion; it has a nervous system; it endures. Is a complicated virus living that needs only a little bit of cellular equipment? Well, maybe. But it does depend on another cell for its procreation. Anyway, I don't have to instruct you, but people simply don't know that.

And so that audience of reporters and other media people didn't know what a virus was or what the genome of a virus is; why it can be infectious. Thirty years later it might still invoke the same kind of uninformed, maybe even incredulous reaction.

Hughes: Did the virus synthesis work mark your first encounter with the press?

Kornberg: On that scale, yes. With the Nobel Prize in 1959 there were all kinds of reporters here and in Stockholm.

Now DNA is known to people. It used to be that DNA in most people's minds stood for an item in motel guides: No Dogs Allowed. Today, with all the attention to DNA, you can go around your community of informed people, highly intelligent people, people who read the Tuesday section on science in the New York Times. Could they give me a clear statement of what DNA does? If one out of ten did I would be very impressed.

Science and the Public

Publicist of Science

Hughes: Have you considered it important to maintain an association with the press in order to keep the public scientifically informed?

Kornberg: I think we should keep trying, even though I think it is almost hopeless. I have attempted to explain what DNA does, what it is, and above that the importance of gaining basic knowledge to solve very practical problems in society, such as health and sanitation and environment. Does the public know that it is a good investment to support the whimsy of people who are curious about facts in nature? If you ask people, would they provide their tax dollars for medical research, 75 or 80 percent say yes. Frame the question a little differently: Major medical discoveries have been derived from the pursuit of curiosity of physicists, chemists, and biologists. Would you provide tax dollars for them to pursue their curiosity about facts in nature? They've not asked that question. Maybe 10 or 20 percent would say yes.

My mission has been to cite chapter and verse as to how the drugs they are taking, the procedures they use--the MRI [magnetic resonance imaging], the X-rays, everything else that they consider essential for their health--derives from such apparently irrelevant pursuit of curiosity. And still the response the next day by them or their legislative representative is, "Hey, we've got AIDS; we've got cancer; we've got this or that disease. We can't afford to divert our limited budget, more stringent than ever, to support someone working on grasshoppers." Or as Clinton said, "I'm not going to approve of grants to work on stress in plants." Had he just thought about it one second more, he could have said, Isn't it important that we cope with stress in plants--drought, disease, excessive moisture, lack of fertilizer?

Unlike science where there is discernible progress, human understanding, social actions are not progressive. Still, scientists as responsible people, like others in society, should respond to opportunities to apply new knowledge to human welfare.

Advocate of Support for Basic Biomedical Research

Kornberg: I'm very much involved in a political effort to get long-term commitment by Congress for support of basic, biomedical research. I was on a conference call last week with a group that is trying to do that, and they were very impressed by the grand scale on which I'm proposing such support. The proposal has some novelty. The scale of the effort would be politically meaningful, unlike current efforts which are amateurish and

ineffective although well meaning, devoted, and capable of occasional victories in skirmishes here and there.

Hughes: How is the reception to your idea?

Kornberg: I've been talking for a year and a half now about a truly major effort for federal support of biomedical research. There may be some movement. There would be more if I were twenty years younger and devoted my energies to it. We have to get leadership. Along these lines, I was chatting with Mike Bishop who is very influential, a great "boy scout" for such efforts. He participates in a caucus that informs congressmen (largely their aides) about advances in science. The caucus informs them about how much is being done, how much there is to do, and how effective science can be for preventing and treating disease. He asked me to survey the number of scientists who would pay dues to a national organization of scientists. Could we afford legislative lobbyists, each at a hundred thousand or two hundred thousand dollars a year?

I said: "Mike, if we're going to do this, don't let's talk about budget. Let's set our goals, what needs to be done, then go to people who have means, including some of ourselves, to see if we can meet those goals with the necessary budget." Mike Bishop and Tom Pollard, who is now the president of the Salk Institute, want very much to do something. They are enlisted, but they lack the courage or dedication to do something on so grand a scale.

Collaboration with Gobind Khorana

Hughes: Were there any significant collaborations?

Kornberg: Offhand I can't cite them.

Hughes: What about Khorana?

Kornberg: Oh yes, I'm glad you brought that up because Khorana was a frequent visitor to my lab. He picked up techniques, learned how to make polymerase and ligase.

Khorana deserves his acclaim and recognition, which has been slow coming from chemists, because the chemistry of nucleic acids was regarded by Robert Woodward and other chemists as rather mundane and unchallenging. What they failed to appreciate was that Khorana was not only doing very solid

and innovative chemistry, but also using biologic techniques that were utterly foreign to them. He was very courageous and accomplished in that. A chemist would not accept the use of an enzyme to carry out some stage in a reaction. Dirty pool; it was beneath them. But Khorana was not above that, and used enzymes very skillfully. He used them to synthesize stretches of DNA and thus made a gene synthetically. I came to appreciate this back in 1956 when I was a guest in his laboratory in Vancouver in British Columbia.

[telephone interruption]

Kornberg: I had a reputation for working very hard, for being unforgiving in wasting an hour or an afternoon, and yet here I was in 1956, at the height of all this excitement about DNA polymerase, going off for two or three months to British Columbia with my family--taking off the whole summer. Several people said, "Gee, how could you do that?" It was unthinkable for anybody, let alone me, to do that. Yet we had gone off repeatedly in summers, escaping the St. Louis heat, taking the family, and in this case really not in the most direct line of our research effort.

We and the Bergs--Paul and his wife, Millie--spent that summer in Khorana's lab. Paul learned how to make an intermediate that was very important in his research. I learned how to make deoxynucleoside triphosphates. There was a very close personal friendship between our families. Later on, Khorana came to St. Louis and still later to Stanford to learn how to make this and that enzyme. On one of those visits we discovered something that was very important, how to make a dAT polymer, the alternating DNA-like polymer of A (adenine) and T (thymine).

Let me mention a discovery that was serendipitous, with major significance. George Beadle and his wife, Muriel (a journalist and historian), wrote to ask about my discovery of the de novo synthesis of DNA (that is, the dAT polymer). Absolutely startling.¹ How did I do it? How audacious. A truly remarkable discovery. I had to tell them that the discovery was fortuitous and serendipitous.

Through the work with Khorana, we established that synthesis of the dAT polymer was not likely a de novo event. It is now heretical to think that you can make DNA de novo,

¹ Muriel Beadle to Kornberg, January 26, 1965. (Kornberg papers, SC 369, box 32, folder: 1965 A-L.)

from scratch. Rather, we now know from the dAT polymer work that such kinds of DNA synthesis are likely to be pertinent to a number of genetically defined diseases in which the repetitious production of a DNA sequence leads to Huntington's chorea or to some other genetic disease.

I think we discovered the basis for that repetitive synthesis, in which a tiny fragment of DNA that contaminated our pure enzyme was then used as a template in a reiterative fashion. We could say that because Khorana had synthesized such fragments. In the paper we wrote,¹ we pointed out how one could explain such apparently de novo synthesis of DNA from a seed that is present as a contaminate of an enzyme.

Changing Emphases in Biochemistry

Hughes: Do you see a trend away from biochemistry in the young people coming into science nowadays?

Kornberg: It's hard to see trends from a narrow perspective or anecdotal encounters. I'd say, yes. [chuckles] As you know, ten years ago I wrote about the two cultures, biology and chemistry.² Biochemistry departments by and large have veered very sharply in the direction of biology. They study very complex phenomena, like cancer, aging, development and differentiation --exceedingly difficult biologic questions. Doing so, they leave the previous domains of biochemistry to the chemists, who take it up to some extent but with their own cultural bias. They look with sharper focus at the chemical structures and try to improve on them. It is an arrogance that may be justified by some results, but to improve on a chemistry that has taken two to three billion years to evolve is difficult to do.

Hughes: What do you mean by improvement?

Kornberg: Chemists think they can make a better enzyme and understand it well enough to endow it with new properties. Take catalytic

¹ A. Kornberg, L. Bertsch, J.F. Jackson, and H.G. Khorana. Enzymatic synthesis of DNA. XVI. Oligonucleotides as template and the mechanism of their replication. Proceedings of the National Academy of Sciences (U.S.A.), 51, 315 (1964).

² A. Kornberg. The two cultures: chemistry and biology. Biochemistry 1987, 26: 6888-6891.

antibodies. Antibodies are highly specific. Could they be engineered to do a catalytic function, then they could do things that enzymes have not yet been found to do.

Hughes: I would think there would also be the danger, in a purely chemical approach, of forgetting the context in which this is happening, namely the cell.

Kornberg: Yes, if not forgotten, then beyond their immediate concern.

To give you a very brief physical basis for what you've said, an enzyme is thought of as a catalyst, right? It brings two molecules together in a fraction of a second which might take years if the enzyme weren't there. It does so at body temperature which might otherwise take high temperatures, hundreds of degrees, to achieve. It is a catalyst. But that's only one of several attributes of an enzyme. An enzyme also has to be regulated, modulated, so that it will act more or less rapidly. It has to be tuned. That tuning gets signals for when it is needed or not. So there is a regulatory face, or domain, that modulates the catalytic activity by orders of magnitude--turns it on or off.

Then there is the social face of an enzyme. The enzyme, as you suggested, is in a social milieu in which its neighbors cooperate to perform some function. Where it sits in the cell, what its neighbors are, how it then responds with catalytic and regulatory activities to the complex biologic situation represents a more communal function.

Hughes: What has moved biochemists away from consideration of the simpler problems?

Kornberg: At least two things. One is the possibility generated by genetics and new techniques to apply chemistry to biologic problems that were previously beyond reach. Animals and cells can be engineered to lack a function or to overproduce a function. These are consequences that couldn't be seen before.

The second reason is fashion. There are always pressures--economic, social, other pressures--to do something meaningful--obtaining a grant, getting recognition from the community and peers, doing something of direct human relevance. The focus on humans has been and is even more so now of greater importance than studies of rats or bacteria. To do the reverse would seem counterintuitive. Yet, we know historically and can prove in case after case that solving difficult human biologic problems has depended on the unanticipated extension of basic scientific

inquiries that had nothing to do with ultimate application to medicine.

I'm saying that it is counterintuitive not only to the average person but to scientists, too, to cope with a disease by studying an arcane biologic system--a grasshopper or whatnot. Scientists as human beings are terribly responsive to what others think. If everybody is crowding and shouting around a certain area, they'll join the crowd rather than be off in some unpopulated area. Biochemistry departments have been renamed Biochemistry and Molecular Biology. There is a shift away from the traditional roots in organic chemistry and intermediary metabolism. Metabolism has become a dirty word in biochemistry. It used to be its core. E. coli (coli), the guinea pig of early molecular biology, is now a four-letter word to funding agencies and the academic community.

The reality of getting money to support students in research is overwhelming. The NIH, which provides 90 percent or more of the support of all bioscience research and training, as well as private institutions, have veered significantly toward clinical and applied research. The support for basic research, in real dollars, has declined in recent years.

Conference on the Chemical Basis of Heredity, 1956

Hughes: Was the conference on the chemical basis of heredity in 1956 a turning point in the direction in which research on the genetic basis of life was pursued?

Kornberg: It was a turning point for me.

In our conversation, I referred to it because of Chargaff's claim that he discovered base pairing. The documentation is very clear. In the talk that he gave at that symposium three years after the Watson-Crick structural hypothesis for replication was presented and widely accepted at that conference, Chargaff ridiculed the hypothesis. He had found the equivalence of A to T and G to C, but he rejected and ridiculed base pairing. Later on when he asserted that he had discovered base pairing, the 1956 conference proceedings documents that that was not the case.

It was on that occasion in 1956 that I presented the first work on DNA synthesis by DNA polymerase. I've looked at that report and it is instructive as to how complex and dirty the

experimental system was. Our subsequent work is an illustration of how pursuit of an enzyme activity can clarify, as we say, lead to clean thinking, when you clean up the enzyme.

Hughes: Meaning, when you clean up the enzyme, you find more information.

Kornberg: Yes. You're measuring the conversion of A to B. You discover that A doesn't simply go to B; it goes through A prime, A double prime, and other intermediates. You discover fascinating things about functions--novel chemistry that had never been observed before by a chemist, let alone by a biochemist.

The conference took place only a few months after we made the discovery. And I know [Francis] Crick was very impressed. Crick, really, is the most successful theoretical biologist. He was very attuned and concerned with the chemistry, unlike the illustrious Caltech figure, Max Delbruck, who was contemptuous of chemistry. Maybe I was too strong, but he thought he could avoid chemistry.

Hughes: Do you remember the reaction of the group at the symposium?

Kornberg: I don't remember. I don't think there was any serious questioning of the results I presented, or any overt doubt that they would lead to something interesting.

More on the Synthesis of Viral DNA

Searching for Biological Activity

Hughes: How consciously were you pursuing the synthesis of biologically active viral DNA to counter the criticism that the DNA that you had synthesized in the 1950s wasn't biologically active?

Kornberg: Eagerly. I'm somewhat pleased to be able to provide evidence that very early on, in 1957, I invited Sol Goodgal, who was studying the Hemophilus influenza transforming principle, to come to St. Louis. In 1959 when I came to Stanford, I collaborated with Lederberg who was working on Bacillus DNA and its transforming capacity. Before that, I had met with Rollin Hotchkiss at Rockefeller. In each of these cases, I was looking, very early on, for assays that would enable us to

determine whether we were making genetically active DNA. And we kept failing. It is now obvious why: we didn't have pure enough template when we isolated the DNA. By the time we got around to using it as template, it had been badly degraded. And there were other enzymes that modified the DNA before it could be used as a template. So there were many reasons why it was a dirty substrate and we were failing repeatedly.

I was being questioned, and even taunted, for many years that, "Yes, you've made DNA but it is not biologically active." Remember, that no one had the means to sequence DNA. And when we presented our nearest neighbor technique to show the frequency with which a nucleotide followed its nearest neighbor in a chain, the information was novel. There was no other method that approached that problem chemically. We could say, well, the DNA we made has the frequency of nearest neighbors that resembles that of the template, the natural DNA. It was accurate within 1 percent, but genes generally have to be correct within 0.1 percent--a thousand rather than a hundred nucleotides. When we finally claimed in 1967--and we were right in claiming--that we had made infectious DNA, it was because we could start with an intact DNA, a circle of DNA, and complete a replica that was circular.

It is ironic that even though we claimed we'd done it, and it's correct that we'd done it, the basis for that claim was flawed. I make that clear in my book. Starting with a circle of DNA, we claimed to have made an intact circle that was a copy of that, and then we could make a copy of the copy, which therefore was identical to the initial infectious DNA. That's correct; we did that. But in the process of starting a circle de novo, we were not actually starting a chain. We didn't know how to do that until five years later. Along with the DNA template, we furnished in an E. coli extract little bits of DNA that served adventitiously as primers. The DNA polymerase we were using had additional capacities we didn't appreciate at the time of cleaning up the product, removing extra bits and pieces, and replacing the initial primer with legitimate DNA. By that time Bob Lehman and his group, and my group too, had discovered ligase, the enzyme that seals, that completes the circle. That was essential.

I've gone into some detail about that in the book, pointing out that even though the product was legitimate, the way in which it came about did have some components that were not properly understood at the time.

Hughes: Well, you were uncovering a very complicated process.

Kornberg: And to be honest, we thought we understood it better than we did at the time.

Hughes: I imagine that is very common in science.

Kornberg: Maybe it is universal that the perimeter of ignorance around a discovery always get enlarged. [laughter] It depends on how much you want to look for trouble, how much you want to delve beneath the level of discovery to discover how thin the veneer is, and find the subsurface where it is still very vague.

Hughes: The new technologies allow you to get into more trouble, as you put it, revealing layer after layer of complexity.

Kornberg: To digress slightly, but pertinent to life in our society, is how our technology has permitted us to detect toxic materials down to levels which are maybe a thousand times below utterly innocuous levels, resulting in an enormous expense to our society--hundreds of billions of dollars spent by the EPA [Environmental Protection Agency] and other efforts, and anxieties that are utterly unjustified.

Arnold Beckman, the nucleating financial source of this Center, deplored that his sensitive instruments were now being used to these unreasonable extremes. Instead of parts per million where you might worry about toxicity, the instruments detect parts per billion, where it is almost homeopathic in its efforts. But I'm saying that technologies are the source of advancing science but at some points they can also be misdirected, misapplied socially. That is quite aside from what we are discussing.

Sinsheimer's Phage Assay

Hughes: In the synthesis of viral DNA, why did you turn to Robert Sinsheimer for the phage?

Kornberg: Well, he had the assay in place in which the DNA was taken up by E. coli. Mind you, this was before Mort Mandel and the plasmid work. With enough DNA, a spheroplast of E. coli (a cell denuded of its outer coat), would take up DNA and could then produce infectious phage. We could have done that, but Sinsheimer had it going in his lab. So we did the biochemistry and we gave him the DNA without identifying what the samples were, and his laboratory could assay infectious units.

Hughes: Was that an unusual step for you to reach outside of your department?

Kornberg: I don't know. I knew him very well. I had other occasions for other encounters, all very friendly and productive. I think it was very reasonable.

Hughes: But was it unusual?

Kornberg: Not really. I just told you about inviting Sol Goodgal, consulting Rollin Hotchkiss, and working with Lederberg. I also consulted Walter Bodmer, who was in the genetics department doing assays of Bacillus subtilis DNA for its genetic activity. I wouldn't say that I was a very active collaborationist--quite the contrary--but there were instances in which someone had assays in place and experience in using them, and the personal relationships were cordial enough; I felt I could trust those people.

Vitalism

Hughes: Was there hesitation, perhaps a reflection of vitalism, to accept the possibility that one could synthesize a biologically active viral DNA, that one could synthesize life?

Kornberg: Vitalism will never die as long as there are systems as complex as cells and organisms; there will be a reluctance to accept reductionism. A valid objection to enzymology in the test tube is that it can't be that simple in a complex creature. We've been over that and it's absolutely true.

I've cited F. G. Hopkins as my hero, and that's his picture [points to framed photograph on wall]. Unfortunately, I never met him. I had reason to go back to For the Love of Enzymes, and I'm pleased I quote him at some length as to his view of biochemistry versus biology, or vitalism versus reductionism. In essence he says that biochemistry cannot explain biologic phenomena, but without the biochemistry, biologic phenomena will never be properly understood. He says it better than that. And that's it: vital functions can be and often are beyond our current capacity to explain them chemically. But every so often, we learn so much that we never anticipated about a biological phenomenon, from very modest, disciplined biochemical or chemical studies.

Right now there is a new vitalism, because now we can knock out genes in mice, or alter them; the transgenic mouse or the knockout mouse is now very popular. And I think it is forgotten by those practitioners that simply because you have a mouse that lacks or retains a genetic function that you know what's going on. That's a new kind of vitalism. You bypass or ignore the lack of chemical details of the process and focus on the end result and try to draw conclusions from that. It provides information, often an extensive amount of important information; it doesn't tell the whole story. You can find that the gene that you thought was essential in humans for making a blood cell or a brain cell is not essential in the mouse; lacking that gene, the mouse is perfectly normal. To be sure, it has gone through an embryonic development in which other genes and their functions have replaced that one. Or maybe that function isn't in the main line, but rather a spur off the main track. Vitalism is something that one has to fight all the time in order to preserve the commitment to do the biochemistry.

Reductionism

Hughes: You've mentioned reductionism several times this afternoon. Do you regard yourself as a reductionist?

Kornberg: I do but only as F. G. Hopkins said, "a reductionist who is mindful of the limitations of reductionism." When you find an enzyme that carries out a function like replication, you don't assume that you know the whole story. And you can be embarrassed to think that you know more about the biologic function than you thought you did. We used to have to rely on poisons, to poison the enzyme in a cell to see the consequence. Now we can do what we call reverse genetics: we can knock out the gene that makes the enzyme; we can also overproduce the gene product and look at the consequences. How valid were our assumptions that we have "the" enzyme and knew what it did? I don't regard it as limiting or insulting that I'm a reductionist, in the context that we need to know much more about events in vivo than what we've been able to reconstrue in the test tube.

There is a great deal of excitement now and adulation of progress made in protein trafficking--discovering how proteins migrate to certain places in the cell to carry out their functions. It is, in a sense, very difficult three-dimensional biochemistry, and a lot of progress has been made. But no one

has yet taken an organelle from which a protein migrates to another organelle (e.g., a Golgi apparatus to an endosome or to a plasma membrane), and taken it apart and put it back together. When anyone succeeds in doing it, a great many revelations will be in sight.

In that vein, with all the elegant virology that's been done, no one has reconstituted a viral life cycle with simple or defined components. If one had done that with any virus, I think we'd be more advanced in HIV [human immunodeficiency virus] research. In fact, a lot of the new excitement about HIV is to find out the receptor to which it attaches. Hey, this is fifteen years later. Why didn't we know that earlier? If attempts had been made to focus on each of the life cycle details, we'd be much more advanced in that field. That's reductionism. With a virus you say, "Well, this is the adsorption protein of the virus; it permits it to attach to a certain cell. And this is its receptor on the cell." Having given them names, twenty years elapses before anyone says: "Well, what is the adsorption protein? How does it work?" There are large gaps in our knowledge. And that's what I might call vitalism too: "You've seen the phenomenon, what more do you want?" "Well, we want to know how it works."

Hughes: Would you go so far as to say that studying protein trafficking, for example, is jumping the gun?

Kornberg: No, I'm not saying that at all. I'm saying that there are stages at which you acquire knowledge but there is also the phenomenon, which I've observed repeatedly, in which people doing cellular biology, genetics--Drosophila and its development--try to solve a serious question. They manipulate the genetics and get new mutants and the suppressors of mutants. Very clever and ingenious manipulations that are highly informative, but they simply don't set up an assay in vitro, a cell-free system, to see if they can reproduce that phenomenon. The essence of biochemistry is that you take a cellular phenomenon, break open the cell, and observe that phenomenon in a cell-free system, which can be subjected to fractionation, purification, resolution, and ultimately reconstitution.

Hughes: Wouldn't they say, if you confronted them with that approach--

Kornberg: Which I have.

Hughes: --well, that is for you biochemists. We're not biochemists; we're geneticists--or whatever they are--and we have a different approach.

Kornberg: And that is what has been said, without naming names, by very experienced and accomplished biochemists who have moved to this other culture.

For ten to fifteen years, others haven't been doing the kind of biochemistry which I just described. We can't get our students and postdocs to do it. They are busy and successful manipulating DNA and genes, and getting invited to symposia and so forth. The very success of molecular biology and the newer cell biology has discouraged people from doing this kind of biochemistry. As I said earlier, that kind of enzymology is not practiced very much. The people who do it are an endangered species.

It isn't simply asking a cell biologist or geneticist to do it. It is asking a biochemist and enzymologist--who used to do that very expertly but is now immersed and oriented in the new culture to direct students and postdocs to do something that is old fashioned or alien.

Hughes: When you were chairman, and perhaps after that, did you attempt to keep research focused on the simpler biologic systems?

Kornberg: Oh, no. Don't confuse being chairman with any authority or responsibility to direct the science. Everybody who joined this department from the very first appointment dictated his or her own direction. Yet, Jim Rothman, who is now the prime practitioner of protein trafficking and gets all kinds of prizes and recognition, has attributed to my example the philosophy and the drive he's displayed in getting cell-free protein trafficking.

[telephone interruption]

Kornberg: I was just going to say in self criticism why am I working on a new subject [polyphosphate] and not engaged in pursuing replication: its physical or biologic basis? There remain a huge number of crucial questions. Why am I fussing around with polyphosphate when I should be clarifying important questions about replication in those directions? You know, these are highly emotional, artistic, personal directions that people take. But looking at it with as much perspective as I can, I believe that there are opportunities in cell biology to reduce complex phenomena by using traditional attitudes along with newer techniques. We call it biochemistry.

Hughes: Let me correct the impression that I think I gave you that I conceived that you would tell people how to do their research. But you can direct by example; you can direct by suggestion;

and to a degree you can direct by the people that you choose to recruit, knowing that there is no guarantee that once they come here they will stick to their approach.

Kornberg: It has got to be very subtle. I had no authority, and on occasion when I questioned an approach or suggested another, it was taken as being over-critical and nonsupportive of the work that was going on. It's a very sensitive issue. And my judgement is fallible. I might be backing the wrong horse. It isn't obvious. One should really do what one believes in implicitly. You have to believe that doing that specific experiment is going to work. And if it fails, that you'll keep at it. So I think anyone who does enzymology with any advice or under constraint is going to fail. It's very rare that you can do something that works early on that you hadn't fully believed in.

Research on Polyphosphate

Attraction to the Field

Kornberg: To this day I'm very eager in the pursuit of inorganic polyphosphate work, which is virtually unknown anywhere else beyond this laboratory. I try to engage others to share our analytic techniques so that they might become interested. In fact, that's the only hope for progress with polyphosphate, because my group is very small and the progress we make is very limited and halting.

Hughes: Why did you go off in the direction of polyphosphate?

Kornberg: Well, it is hard to describe. For the sake of being entertaining in giving seminars on polyphosphate, I give one of the reasons. I have a slide that I introduce early in the seminar, and I've used it repeatedly, that has to do with an event that took place a dozen years ago when I gave a seminar at the University of Wisconsin in Madison. I was about to present what I thought were very exciting results on the start of a DNA chain, and it led to a whole series of investigations that I'm very proud of.

But in going from one lab to another as one does before giving a seminar in the afternoon, I entered somebody's office, whose name I can't recall, in which I saw on the blackboard this statement: "Seminar today by Arthur Kornberg at 4 P.M. on

you know what." [Chuckles] It crossed my mind that I would some day like to talk about something that they don't expect me to talk about. There was the wish to do something different from what I'd been doing for forty years.

There was also some nostalgia and sentiment. My late wife, Sylvy, and I had found an enzyme that made a substance that was very much in people's attention then and very baffling. It was this polyphosphate chain. At that time, ATP and something that had ATP bonds, called high energy bonds, were very much in people's minds. Inorganic polyphosphate, with many hundreds of phosphate linked by such high-energy bonds, was a molecule that people knew existed in cells, probably existed prebiotically, very early in evolution of molecules on earth. It was called a molecular fossil because it had been around from the beginning of time and nobody knew what it did--presumably nothing.

So in 1955, in the heat and excitement of discovering how E. coli was such a fertile source of so many things we were discovering, I said, "Well, we know how to label ATP. Is there a chance that ATP might generate polyphosphate with one of these extracts?" And it did!

Rejection at Berkeley

Kornberg: And I again say, for the sake of entertainment, that in late 1955 I was invited to give a seminar at Berkeley that might identify me as a person they'd want for a position. I was so excited about the polyphosphate work, that instead of talking about our embryonic studies on DNA replication, I talked about polyphosphate with all the enthusiasm I could engender--and I didn't get the job. [laughter]

Now, people at Berkeley, including my revered senior friend, H. A. Barker, after whom there is a hall named, said, "Well, Arthur, you really didn't consider the job seriously. Even if they'd offered you the job, they didn't think you'd take it."

Hughes: Was that true?

Kornberg: I don't know. Others might be better able to judge that. Dan Koshland in his very typically humorous, almost flamboyant way deplored Berkeley's not having offered me the job.

The person they chose was absolutely outstanding; he's really one of my heroes in biochemistry, Esmond Snell. I think at the time I would also have chosen him over me. Snell's achievements in biochemistry are extraordinary but they were not as glamorous as mine; they didn't get the popular attention. He worked on molecules that weren't as sexy. But I think his biochemistry was every bit as profound and significant.

We had made that polyphosphate discovery in 1955, but then the DNA replication work took over for the next thirty-five, forty years. I was aware of polyphosphate--you don't forget things like that; they're part of you--but I never did anything about it. And then I had a bright postdoc chemist, Kyunghe Ahn, who had done a postdoc at Berkeley with Judith Kleiman in chemistry. But Kyunghe had had to come to Stanford because her husband got a job here. Anyway, the project she was working on wasn't going well, and she said she'd like to purify an enzyme. I said, why don't we go back to this polyphosphate enzyme. She did a great job in purifying that enzyme.

My interest in it grew for the several reasons I've mentioned and maybe other reasons. I had former students, some of whom were very accomplished, working on replication, and I'd be doing something similar, competing with them. So I saw this work on polyphosphate as an opportunity to do something different. I've learned that you don't mess around trying to do two different things. You try to do something, and do it well. So I decided I would phase out the work on replication and devote myself to polyphosphate.

Now, five or six years later, was it a good choice to have been I'd say yes. I should have done it sooner.

Hughes: Why do you say sooner?

Kornberg: Well, because I don't have that much time left, or the energy or drive that I had ten years earlier.

Hughes: But you would have also spent less time on the DNA problem.

Kornberg: But I'm saying that that problem was already being pursued by my students elsewhere in the world.

I gave a lecture in Tokyo about ten years ago--and I'm going to give a lecture in San Antonio with the same title--"DNA Replication from Start to Finish", with the intention of describing current and exciting work on how the chromosome is completed; how it terminates; how it is finished. I was

greeted at the airport by a former Japanese postdoc, Kazuhisa Sekimizo, who seemed disturbed about the seminar I'd be giving. I said, "What's the trouble, Kazu?"--a nickname. He said, "Well, its the title of your seminar." I said, "What's wrong with it? I'm going to talk about this exciting new work that Jung Lee is doing on termination." He said, "Yes, but when my professor"--remember, in Japan a professor has a great deal of authority--"saw the title of your talk, he said, 'You must stop working on DNA replication because Mr. Kornberg says it is all finished.'" [laughter]

It was far from finished then or now. But I'm pleased with the polyphosphate work because I think we've made substantial progress, developed new methods, and it has given me the incentive to be more attentive to the work.

There is a piece written up in Stanford M.D. [Winter '95-96] which quotes one of my postdocs coming back from a long weekend and saying to the group, "You know, this weekend I found myself thinking more about the polyphosphate work than I did after a similar weekend when I was working on DNA replication." And this Chinese postdoc chimed in, "Of course, you behave as if you're trying to get tenure." [chuckles] So that reflects the fact that I do feel more responsibility for this polyphosphate work--responsibility to myself and to my people who have either been hoodwinked or of their own volition are working on a problem that's very much off the beaten path.

As I mentioned a few minutes ago, I am trying to get collaborations or to help other labs work in this area. The work is much more exploratory; it is not done in the depth that I worked on in replication. It is more physiological. It is our responsibility to show why polyphosphate is important. We didn't have to do that with DNA. Anything we did on the enzyme that made DNA was already noteworthy and attention-getting. People say, "What is polyphosphate? Never heard of it; don't care about it." So the only way to make people care is to say, "It's important in some disease, say meningitis."

Medical and Developmental Implications

Kornberg: Polyphosphate forms the capsule of Neisseria meningitidis, also Neisseria gonococcus--gonorrhoea. If you knock out the gene (in that organism) that makes polyphosphate, they are much more vulnerable to being destroyed by human serum. Which may be important in the pathogenesis of those infections. Nobody I

know has taken up on it. There are numerous examples where I believe polyphosphate is carrying out an important function.

The contribution we've made that I'm pleased with is in the aging of E. coli--meaning when the coli culture stops growing because it has run out of nutrients or has toxic elements. If it kept going, it would be the size of the earth in a couple of days. So why does it stop growing? Well, that's another matter. But now we find out that when we create mutants that don't have polyphosphate--because they don't have the enzyme because we've knocked out the gene--they die in this stationary phase. Coli wouldn't be here today if it didn't survive under stressful and deficient circumstances; call it aging in E. coli. How does it cope with stresses and nutritive deficiencies and toxins? All I can say now is, polyphosphate is an important part of the network of responses to stresses. We're trying to get down to the molecular details of how it does that. I think that's exciting. It doesn't persuade people to drop what they're doing and work on polyphosphate--yet.

Unpopularity of the Research Field

Hughes: Do you have problems attracting people to do polyphosphate research?

Kornberg: Oh yes. Yet, the people who have worked on it have gotten good jobs doing something else, because of the training they've gotten and the achievements they've made identify them as being very able scientists, and that's what matters most. But I've had trouble attracting eager people. The fact is I'm seventy-nine years old. Why would anybody work with somebody that old, with that limited energy and that limited future? I'd rather work with my sons Roger or Tom. They're at the height of their productivity and their careers.

Hughes: But surely scientific experience counts for something.

Kornberg: It counts for something. Yes, I don't think I'm utterly unproductive. I think there are things like judgment that come with maturity.

Another reason why people aren't attracted to polyphosphate research is the obscurity of this molecule and the problems that surround it. It has repercussions because if a postdoc leaving here applies for a grant to work on polyphosphate, I

think the chances are, especially in today's funding climate, that he would not compete with someone working on an oncogene or signal transduction or any of the fashionable subjects. If he were lucky, someone on a committee might feel persuaded to say, Hey, this is an interesting molecule--it's in our brains; it's everywhere. We don't know what it does. Shouldn't we find out something about it? What are the chances then that this grant applicant will be able to tackle and sustain an effort in that direction, and attract students and postdocs to work on it?

It is illustrative of the problem of doing something that is pioneering or unorthodox or novel. The climate in science has been, and is even more so now, unreceptive to things that are labeled courageous and could be foolish, unproductive efforts. One of the great flaws in our granting system is that it is poor in support and sympathy for doing something that might turn out to be unproductive.

More on DNA Polymerase

Early Interest in Nucleic Acids

Hughes: Dr. Kornberg, in your papers in Green Library I found evidence dating back to 1947 of your interest in nucleic acids.¹ Do you think this was the first year that you began to work on nucleic acids?

Kornberg: [skims documents] Well, Sally, in 1947, I had just returned to the NIH, and really had no direct knowledge of or particular interest in nucleic acids. I had done work in St. Louis that I was going to extend at the NIH regarding a coenzyme which we called DPN, now nicotinamide adenine dinucleotide--renamed NAD. I was pursuing the purification of an enzyme that split NAD into its two components, one an adenine nucleotide, called AMP, adenylic acid, and the other that bore the nicotinic acid, the vitamin component--nicotinamide ribose phosphate, a nicotinamide mononucleotide (NMN).

As I've described in the book, For the Love of Enzymes, purifying the enzyme that split that coenzyme led in a series

¹ Kornberg to Floyd S. Daft, Chief, Nutrition Section, NIH, December 18, 1947. (Kornberg papers, SC 359, box 15, correspondence 1947-1949.)

of further studies to an appreciation of how coenzymes were made from their building blocks, and then to a curiosity about how nucleotides were assembled into what were then mysterious structures, RNA and DNA. I would say certainly, around 1950, I became seriously interested in nucleic acids, for these reasons.

Also I remember advising my close friend and colleague, Leon Heppel, who was going on a sabbatical to work with Roy Markham in Cambridge, England to pay attention to nucleic acids, work that Markham was already involved in. Leon Heppel's career thereafter was shaped by his studies of ribonuclease and how it acted. It would be very worthwhile to talk to Leon Heppel, who at eighty-five at Cornell is working more vigorously than any student or postdoc there.

Anyway, I date my curiosity or interest in nucleic acids to about 1950, but I didn't do much on them until sometime later. Again, as I describe in my book, I looked at nucleic acid and wondered for the first time about how it was put together. I became aware of the linkage of phosphate between two sugars, called phosphodiester, that is the backbone of RNA and DNA.

I was then alerted by a paper that had just appeared on the accumulation in liver of a very simple molecule, a structural element of phospholipids, glycerophosphorylcholine. The phosphate links the alcohol (glycerol) to choline. So I set out to explore the biosynthesis of that compound, thinking that that would be a model for how a phosphodiester is made. I thought it might be a model that would help understand nucleic acid assembly; that led to other events that I won't belabor at this time.

Hughes: So your interest in nucleic acids arose later than 1947.

Kornberg: Yes. In 1947-48, Floyd Daft, chief of nutrition at NIH, had been my immediate boss from '42 to '45. He was a chemist by training but then became very oriented toward nutrition and physiology and was very interested in and active in the actions of folic acid. In fact, I was the one who years later discovered the enzyme in which folic acid is involved in the synthesis of thymidine or thymidylic acid.

At that time, it was known from nutritional studies, I think largely microbial nutrition, that if you fed a microbe thymine, it partially eliminated the need for folic acid. So the implication was clear that folic acid was involved in the synthesis of this nucleic acid component. Daft had some ideas that I thought were either far out or inaccessible for testing.

I regarded his very veiled suggestion to me that I look into the nucleic acids as an imposition. I knew so little about them and the field was so messy, I didn't want to have much to do with it.

Hughes: What do you mean by messy?

Kornberg: Well, there was no biochemistry, and the chemistry of the nucleic acids was also vague--it was more vague to me than it need have been. No one knew the size of the polymer or its sequence. It was messy compared to a homogeneous entity with a defined chemical composition. It was messy and remained that way for many years.

More on Chargaff's and Avery's Contributions

Hughes: Was Chargaff the main name in the field at that stage?

Kornberg: Yes. I don't know whether he had done his work by '47 or '48--we'd have to look up his papers--but chromatography had become available. He was able to subject the breakdown products of nucleic acid--let's say DNA--and examine the composition of the four distinctive bases, A, G, C, and T. He made the remarkable observation that DNA from a given species had an equivalence of A to T and G to C. When he looked at the DNAs of various species, the ratio of A-T to G-C varied--a very profound observation.

Hughes: Why was he looking at base ratios?

Kornberg: I think he had an interest in nucleic acids from a much earlier date. He was a chemist and the essence of biochemistry, certainly in this country and among some chemists in Europe, was analytic: you wanted to know what the composition was, and that was a feat in itself. Chargaff was not in the group that was introducing dynamism into biochemistry. There were people like [Rudolph] Schoenheimer and others who were using isotopes to show how molecules, proteins, turned over; and there were others who were using enzymes. Chargaff was not in that group of [Otto] Warburg, [Herman] Kalckar, Cori, [Fritz] Lipmann, and others who were interested in how energy was used. On the other hand, that group was not interested in nucleic acids. They worked with carbohydrates, sugars, coenzymes, and enzymes.

Hughes: Chargaff wasn't interested in the nucleic acids as potential informational molecules?

Kornberg: He might have been; one really should find out from his writings. I don't know where Chargaff stood, and I wouldn't trust what he had to say years later. You would have to read his papers, which are available. What did he say at the time?

More likely than geneticists or people outside of New York, he must have been aware and may have been impressed by the findings of Avery and his people which were published in '44. New York was a small place in terms of science, and Chargaff must have been struck by the Avery work which identified DNA as the genetic material. I would think by the mid-forties, Chargaff might have focused on DNA because of its importance in heredity.

Hughes: Yet the significance of Avery's work is said not to have been appreciated at the time.

Kornberg: Not only not appreciated, it was criticized, maybe even ridiculed, that a molecule so ill defined and monotonous and simple could be the source of hereditary information. Alfred Mirsky, a very outstanding and influential person in the Rockefeller Institute, openly opposed DNA as a source of hereditary information. He held that in Avery's experiment, the DNA contained proteins that hadn't been detected and that they would surely be the genetic stuff.

More on Viral DNA Synthesis

Use of the Term 'Genetic Engineering'

Hughes: The other subject that we talked about was the enzymatic synthesis of viral DNA. One of the consequences of that work was that you were pulled into some debates. A lecture which you gave in 1967 at the University of New Hampshire was called, "The Recent Revolution in Biology." Do you remember it?

Kornberg: No.

Hughes: You introduced your talk by asking, "We are face to face with genetic engineering. Is that good or bad?"

Kornberg: In '67...

Hughes: In '67. That term was being used then?

Kornberg: I remember using that term at Washington University on some occasion; it might have even been earlier than that. And I was cautioned by someone at the reception following my lecture that it didn't sound good. "You ought to find another term than 'genetic engineering.'" And years later, biotechnology got to be the euphemism for it.

Trying to Produce a Biologically Active Molecule

Hughes: 1967 was the year when you announced the biosynthesis of viral DNA.

Kornberg: That was in December.

Hughes: Nonetheless, you must have been thinking about it earlier in that year.

Kornberg: I'm pleased to know I was thinking along those terms in '67, because as you know with the Peter Lobban affair, we didn't come out so well as predictors of the impact of these techniques.

Hughes: What prompted you to be thinking that way?

Kornberg: I don't remember. [laughs] Remember, that soon after we knew we could put DNA together, or copy DNA, then immediately the questions were: how good is this enzyme at doing it and could it make biologically active and genetically active DNA? I was very bold and maybe foolish to think we could do it quickly. So I got in touch with Rollin Hotchkiss, who was a specialist in pneumococcal DNA transformation, and Sol Goodgal at Hopkins at the time, who was doing a lot of work on Hemophilus influenza.

Then when I came to Stanford in '59, I collaborated with Josh Lederberg, A. Ganesan, and Walter Bodmer, who has written about this and me in one of his recent memoirs. We were looking for transforming activity in our synthesized DNA, using transforming DNA as template. We kept failing--and we failed repeatedly. Whether we had the idea that if we could copy DNA in the test tube, we could engineer it, I can't recall.

Hughes: You must have been deeply engaged in the work on viral synthesis when you gave the lecture in New Hampshire in 1967. So don't you think the possibility would have been in your mind of producing a biologically active molecule?

Kornberg: I'm saying we had been trying for ten years. It is difficult to tell how one takes credit for doing things that turn out to be wrong or more complicated than one imagined. That applies to viral DNA synthesis.

After the hubbub subsided, some months later we realized that we hadn't made an intact DNA circle from scratch. DNA polymerase I, though we tried desperately to show that it could start a chain, couldn't start a chain. So how did we start a chain on the single-stranded viral genome? That remained a mystery for four or five years.

The reason we could make a circle was that a new enzyme was discovered called DNA ligase. It was discovered by Bob Lehman and his group next door to my laboratory in which Nick Cozzarelli was doing similar work, and it was discovered by two labs in the East, by Marty Gellert and I think Charlie Richardson. Anyway, within months, four labs working independently found this enzyme that could link two ends of DNA, and therefore was called ligase.

The DNA synthesis to complete a circle depended on that enzyme. But that enzyme was still impure. We had to add a crude fraction from E. coli to make the ligase work. That crude stuff was the source of fragments of DNA that primed the start of a synthesis that polymerase then exploited. Polymerase had functions we didn't fully appreciate. It had two additional capacities: one to remove nucleotides that didn't fit (i.e., didn't match) at both ends of a little piece of foreign DNA. So picture some fragments of DNA that fortuitously in some stretch paired with the viral genome circle, but at each end didn't pair. DNA polymerase was able to tailor those ends and remove those unmatched regions--utterly unanticipated.

In subsequent years we proved that DNA polymerase I couldn't start a chain; it could edit, proofread, and tailor the mismatched ends of DNA. We ended up not knowing how a DNA chain is started. I'm proud that we finally solved that problem. I can also be embarrassed that we thought we'd solved that problem and hadn't, and that it took so many years to do it.

Hughes: Would you go into detail about how you got the ligase to work?

Kornberg: The chief credit for that goes to Bob Lehman and Toto Olivera, a postdoc. The ligase they were working with requires NAD. But that was not known at the time; it was known that a crude coli fraction could do it, and they later showed that it

supplied the NAD. The crude fraction is described in my paper as boiled juice (called in the old literature, "Kochsaft"), a favored source of coenzymes or cofactors needed by enzymes, but unlike enzymes, were not destroyed by heating. (Incidentally, some other ligases use ATP rather than NAD.)

To repeat, the boiled E. coli juice supplied both primers and the NAD needed by ligase.

Hughes: None of which you could appreciate at the time.

Kornberg: No. We thought that polymerase I was starting a chain. We tried so hard to find the start of the chain and couldn't find it. Then it dawned on me that polymerase I was not starting a chain and that primers were being extruded by the polymerase.

Early Concerns About Genetic Engineering

Senate Testimony, March 1968

Hughes: In March 1968, you testified before the Senate Subcommittee on Government Research on the "ethical, social, legal, economic and political questions which are implied by...the replication of the DNA molecule."¹ Was it your work on viral synthesis which brought you to the Senate's attention?

Kornberg: I would think so. As you know, there was a great hullabaloo that surrounded this announcement, and people misinterpreted the significance of what we had done. Being able to synthesize a "hairy creature," such as a virus, that gets into you and makes you sick, conjured up all kinds of imaginary problems, not unlike the recent fuss about the cloning of the sheep, Dolly. So that had to be set straight, but still there were reverberations from the announcement that one could create life in the test tube, even though people were unprepared to define what life is, let alone distinguish between a virus and a bacterium. So again, much like the sheep cloning, it caught

¹ [Senator] Fred R. Harris to Kornberg, February 26, 1968; Statement of Dr. Arthur Kornberg, professor and executive head of the department of biochemistry, Stanford University School of Medicine, Palo Alto, California [n.d. but March 8, 1968]. (Kornberg papers, SC 359, box 2, folder: Senate hearings 3/8/68.)

people's attention, and I am almost certain that's why I was asked to testify on this occasion.

Hughes: [Abraham] Ribicoff appears to have been your main questioner. Do you remember his demeanor?

Kornberg: Not at all. I'm sure it was very friendly.

I'm struggling to distinguish this appearance from another occasion which I would guess was around 1972. There was a committee, about a half dozen of us, that Mahlon Hoagland chaired. Then I remember an encounter with senators that were not that sympathetic to basic research. I remember telling somebody in defense of basic research that that's how we got the polio vaccine. And either the young legislative aide didn't know what polio was, or might have said, "Okay, but what have you done lately?" I was unable to convey the dimensions of the new discoveries in molecular biology and genetic chemistry because we simply couldn't anticipate their applications.

There was a senator from Massachusetts, not [Ted] Kennedy, who said, "Yes, doctor, we know that we need more information to tackle cancer, but that is what the automobile manufacturers told us with regard to some device or other. We put their feet to the fire; we got results." So I couldn't persuade him that this wasn't simply a matter of engineering, but that there was a lot of fundamental information lacking without which Nixon's call for a crusade against cancer would certainly fail.

Critics of Genetic Engineering

Hughes: In the 1967 Spaulding lecture, you made a reference to Barry Commoner, who was already talking about the hazards of genetic engineering

Kornberg: What did I say?

Hughes: You said, "In recent months, Barry Commoner has been making headlines about the hazards of genetic engineering." The reason I'm bringing this up is to illustrate that concerns about genetic engineering arose prior to 1973. Do you remember why Barry Commoner was involved in this issue at this date?

Kornberg: No, I don't. If I want to be nasty, I can say that whenever there is an occasion that has some controversial component,

someone who takes a posture that arouses fears and is perceived by the media and the public to be newsworthy because catastrophe will get a lot of visibility. I question anybody who has taken these extreme views about genetic engineering, and gained headlines from it. They are either misinformed or devious or maybe innocently express a fear, and that is massaged by all the attention that he gets.

There is another guy, [Liebe F.] Cavalieri. He's really odious. I felt so angry. I had intervened and helped him retain a position at Sloan Kettering and vouched for him in terms that validated or even exaggerated his stature as a scientist; and then he did the very thing that I'm describing here. He jumped on some bandwagon, perhaps led by Commoner and people like that, and then became widely quoted about the dangers of genetic engineering. There was also Chargaff, and others too.

Hughes: What about Sinsheimer?

Kornberg: Sinsheimer--inexcusable. Any number of people have since not only been silenced, but they have used these genetic engineering techniques, otherwise they would have had no future in science. I want to say it as loudly and clearly and as frequently as I can, that today in 1997, twenty-five years after these techniques became available and used in millions of experiments by the clumsiest and most inexperienced people, there hasn't been a single incident of any harm done or anything questionable regarding anybody's welfare. And you can be sure that had there been one such instance, the Jeremy Rifkins and the current versions of the Commoners and Cavalieris would have pounced on it; it would have been a vindication of their predictions of disaster. And it hasn't happened. It's astonishing as I say or quip that it has clearly been less hazardous than slicing bagels. [laughter]

Benefits and Dangers

Hughes: In retrospect, it is evident that nothing untoward has come from this technology. But a critic might say, when this technology was first appearing, you didn't know for sure what it might create.

Kornberg: People who are knowledgeable in infectious disease, which the Asilomar group was not, and people who are astute in plant and animal breeding could have pointed out that these techniques

couldn't come close to creating the kind of difficulties or damage that goes on every day in nature, either with unplanned or planned breeding. To develop an infectious organism takes countless generations of adaptation. So yes, if a scientist was asked as I was, "Doctor, can you assure me that something couldn't possibly go wrong in the use of this technique?" I'd have to say, "I can't assure that something couldn't possibly go wrong. If you go down to your mailbox, can I assure you that you won't break a leg?" It seems unlikely but it could happen.

So what are the relative dangers, and what are the relative benefits? This technology is not being applied out of pure curiosity. As I say in this testimony, if you have a genetic disease or are threatened with having one, you want to be able to cope with it, or avoid it, or correct it. And this is what these techniques can conceivably do. And in fact they've done that.

Hughes: You were quite convinced at the time that new pathogens could not be created?

Kornberg: I'm not going to say that; I don't know. I'm saying that alarmists get a lot more attention than people who are sober and analytic and reserved. You read about salmonellosis, Salmonella infections of chicken and hamburger meat and whatnot. That problem could be solved so simply by radiating food, a process which is utterly harmless. And yet, the FDA, because of popular concerns about radiation known to damage tissues, should agree that it is utterly safe to radiate meat or chicken or fish to kill bacteria.

The FDA has demanded the identity of products of radiation of meat to see what levels can be tolerated. But there are no detectible products from this radiation. The DNA gets broken, and that's why it kills bacteria. But no radiation products accumulate; you can't find them. The FDA insists: "Find them, and determine the toxic levels of these products." "But sir, there are no products." "Well, we won't approve of radiation without knowing them." A "Catch-22."

And now the chefs of America say they will not use a bioengineered product. How stupid can people be? No one is prevented from engineering a whole fruit or tomato by simple grafting.

Hughes: One factor is the poor level of scientific understanding in the public domain.

Kornberg: I think we're always going to be faced with the human element of basic lack of understanding or intelligence or a habit of mind in which disasters, no matter how tiny the risk or how improbable, will take precedence over a sober assessment of whatever level of danger there is.

The Nobel Prize

Stardom

Hughes: Turning to what I hope is a happier subject, the Nobel Prize. Do you have a comment?

Kornberg: I've said this in another context. I've been rich and I've been poor; rich is better. So it's much better to have won a Nobel Prize than not to have won it. And that applies to the anxiety and bitterness of those passed over in favor of others who were less deserving.

I was in La Paz, Mexico, a few weeks ago, and it was the first visit of a Nobel laureate in the history of Baja California Sur. In some areas of the world, such an appearance has a rock star quality. Is that good or bad? Since we bemoan the excessive adulation of movie and athletic stars, isn't it better to have scientists identified with stardom, even if it isn't fully merited? Unfortunately, many more deserving of the prize have been passed over than those anointed.

It struck me some years ago to vindicate some of the Nobel Prize committees' choices that I questioned. It is not widely appreciated that the choice is not made on the basis of productivity over a number of years, but rather for a discovery. How else to justify that someone who has done nothing of significance before or after the cited discovery is given such recognition? The justification, I've decided, is that the Nobel Prize has a lottery quality to it. Someone can go into the lab and say, "If this experiment works, I could get a Nobel Prize for it." It may be one in a million, like a lottery. There is glamour attached to something that can be reached by almost anyone.

Hughes: So you look upon the Nobel Prize as an incentive to scientific achievement?

Kornberg: To many people it is. And some people's lives have been ruined by their hopes and frustrations, hopes for the prize and frustrations in being passed over year after year.

Mistakes of Commission and Omission

Kornberg: Alfred Nobel stated that the prize was to be awarded for a significant discovery in that previous year. It has been broadly interpreted to include discoveries that were made many years earlier and became known later.

I don't want to criticize the Nobel committees. They've made mistakes of commission and also omission. For example, Oswald Avery, who lived for ten years or more after he made the discovery that DNA is the basis of heredity, didn't get a Nobel Prize. And there are other examples. But the Nobel committees work very hard, and I think it's the most diligently researched and worked over choice compared to any other award committee or honorary degree committee.

Factors in the Nobel Committee's Decision

Kornberg: I know a little bit about the workings because I've had a very close friend who has been involved, Peter Reichard. Nominations are solicited from a thousand different people, and are then winnowed to a small number. During the summer preceding the awarding of a prize, committee members take home thick folders and go over them in great detail. A nomination may incubate for many years. The discovery has to be utterly sensational and overwhelming for a prize to be awarded after a nomination in the same year. I don't know enough about that, but I would think so.

The other aspect that is undesirable or unfortunate is that there is an element of timeliness. The discovery has to be at a moment when the spotlight is in focus on the field in which the discovery was made. If time passes and the spotlight shifts, a great discovery can be ignored.

And then the committees are very small, and a vocal influential member can have a disproportionate influence pro or con. He can say, "Look, forget this person;" or, "let's give this person the most serious consideration." Or, "If we give

it to A then we've got to give it to B and C," and that immediately invites some kind of dissent. And then, "If you give it to A, B, and C, how about D? D is deserving." "Well we can't give the prize to four individuals. So let's give it to A or not give it at all." There are a lot of politics of that kind, but generally not driven by ethnic, geographical, or national interests. Perhaps Scandinavians have gotten a disproportionate number of Nobel Prizes. But then their work may be better known to the committees. But largely, the prize hasn't suffered from politics or prejudice.

Hughes: Do the prizes tend to go to the hot areas because they are the focus of attention, or is there an intent to award the prizes in areas of current interest?

Kornberg: Aren't you saying the same thing?

Hughes: I mean in the second case that the committees have determined to award the prize in areas of current interest.

Kornberg: The two approaches merge so considerably that I really can't see a distinction.

Kary Mullis is identified by a federal district court in San Francisco as having been the inventor of PCR, and clearly was a major factor in that discovery. When you investigate the basis for that discovery, you find that it wasn't that novel or original. But PCR has had such a profound influence that the Nobel Prize committee felt that they had no choice but to give the prize to him. He certainly doesn't represent an image for science or scientists that is healthy and desirable. And he is one of the scientists who has never done anything before or since, and never will.

Look, anytime you have people, you have politics. The Nobel Prize committee in chemistry has been vilified, excoriated, by my colleagues here in chemistry who will say, "We never heard of the guy. He's a biochemist." I say, "Well, that's your problem. You should have heard of him." There are vicious letters from chemists to the committee. Well, the committee is made up of colleagues, and they are not immune to criticism. So the next time, they're not going to do something that controversial. They'll play it safe. They'll give it to an organic chemist who is very well known and deserving.

As I said earlier, within a group of five people there is bound to be somebody who is more vocal, influential than someone else, and very persuasive pro or con. You have to remember that the decision didn't come down from the heavens;

five guys were working at it, with all kinds of pressures and persuasions and whatnot, and have to select somebody. Nevertheless, through its public relations, its image, the traditional respect given it, the Nobel is the most sought-after scientific prize. And I simply say that I was very lucky to have gotten it at an early age.

Drawbacks

Kornberg: On the other hand, it disqualified me for any number of other prizes I might have gotten. That's the downside.

Hughes: Are there any other downsides?

Kornberg: Well, I've hinted at it. You're instantly a sage, someone to be quoted as taking a position on issues in which you're not qualified--social, political and economic issues. And that's uncomfortable. In the case of some benevolent issues, I'm asked: "Aren't you supporting thus and so, this society or this declaration." And I've said, "You know, a few weeks ago, no one asked me and suddenly I'm being asked." "Well, look, things have changed. If you don't support it, it means you're against it." Or, "If you're silent, it means you've been asked, but you have reservations about it."

I'm not a Zionist. But I'm very supportive of the state of Israel. But now I'm asked to do very pro-Zionist things or to make statements. I'm uncomfortable; I'll say, "Well, I didn't do that before," and then the reaction occurs that I've mentioned.

And then, you associate with other Nobel laureates, a little elite group. And again, I'm not comfortable with that. It's a coterie. These people have been anointed, and I'm anointed too, and so it's a little club. There was a Nobel Prize jubilee four or five years ago, the ninetieth anniversary of the prize, and we were all invited to Stockholm. I'd missed an earlier jubilee and was told it was a great party. I went this time and I didn't enjoy it--a lot of people strutting around and wanting to be regarded as important.

I don't want to pick on the Nobel Prize. I have been in the National Academy of Science for forty years. I've gone to only one meeting. There are very decent people, my friends, who like to go every year and enjoy the social and other interactions. So I'm revealing an aspect of personality that

I'm neither boasting about nor ashamed of. In fact, I served on the Council of the National Academy in the mid-1960s, and although those meetings are held immediately before the annual meeting, I never stayed for it. I've been a member of the American Philosophical Society for many years, but I've never gone to a meeting.

In fact, I'm told now by so many people that it must be true--former students, postdocs, who are now aware of the extent to which I'm traveling--that I never traveled for all those years, the fifties, sixties, seventies. I was well known to have been represented at meetings by my students and postdocs, but I didn't go myself. I gave some lectures but nothing like what I'm doing now. I had not been involved in national affairs in science, which require that you go to meetings, be visible, and make friends with nominating committees.

Professional and University Service

Hughes: That pattern reinforces your statement that you don't particularly like elite groups. But doesn't it by implication also say something about your dedication to science?

Kornberg: I wouldn't go that far.

Hughes: Why not?

Kornberg: Well, you can infer that. I think it also applies to my involvement in administrative affairs within an institution. I left the NIH when I felt threatened with becoming part of some higher administrative structure which I found very unappealing. And then I've been invited to either be or be considered for a deanship in one place or another. That has not been appealing. I ran a department for many years in a pretty democratic way, and when I stopped being chairman, it didn't change my lifestyle. I haven't been involved in university politics. I've never been a member of the [Academic] Senate or on any influential committees, aside from a number of search (faculty selection) committees.

Hughes: How do you explain that?

Kornberg: Let me explain it in two ways. One is that people didn't expect me to be a useful member of such a committee [chuckling]; that I wouldn't give it the proper attention.

Maybe also a lack of personal popularity. Or it could have been in some instances it was well known that I didn't want to be on such committees.

Certain people emerge as politically skillful and they may be very helpful and effective. But they are politically conscious; they don't offend people; they are interested in details; they attend the meetings. I've not been that kind of animal. And there are times when I should have been. I could have made a difference in the medical school, the university. But it takes effort. Politics is a full-time job. And there are scientists who are skillful enough so that they can do this to a sufficient extent to be well known and influential and still maintain a reputation in science. Very difficult to do but they do it. Having said all that, I do enjoy some considerable concern about public issues and as an evangelist for science. And I'm doing more now than I used to.

Scientific Repercussions

Hughes: What about the effect of the Nobel Prize on your science?

Kornberg: I don't think it had any effect. Unlike perhaps the vast majority of other laureates, I was very young when I got the prize. I didn't take it seriously. It didn't alter what I was doing. Some Nobel laureates would say, "Well, I've got the prize for having done this, now I have to do something different to indicate that I can make another discovery, or that maybe I'll get another Nobel Prize." I will say with as much conviction as I can that it did not alter the quality or quantity of what I was doing. People were surprised, and maybe I should have been too, that it came so early.

Severo Ochoa, with whom I shared the prize, in many people's minds because I was his student, got credit for work I did long after I left him. This last Monday I was in Kansas City to honor Santiago Grisolia who came to Ochoa's lab about the same time I did. He was being honored for his contributions to that medical school. So it was an occasion to discuss our inspired teacher and his contributions. People still believe, because that's the citation that was read at a lecture in Kansas, that he was awarded a Nobel Prize for discovering the synthesis of RNA and I for DNA. That is not the case. His discovery was for an enzyme that degrades rather than makes DNA.

Yesterday, that damn enzyme, polynucleotide phosphorylase, hurt me again. My postdoc in pursuing another observation relevant to inorganic polyphosphate was confused (and I with him) by measurements and assays that we attributed to a novel enzyme and which proved to be the very same enzyme that the Ochoa group discovered. That happens many times. So that was the occasion for discussing that enzyme, which is infamous in my memory. With Ochoa's discovery of that enzyme, I abandoned a promising start in the discovery of the true RNA synthetic enzyme, RNA polymerase.

Hughes: What about the prize's influence on your science?

Kornberg: I'm trying to say that it had no influence.

Hughes: No? I could speculate, for example, because of the spotlight that the prize throws on an individual, that you may have had more applications from postdocs.

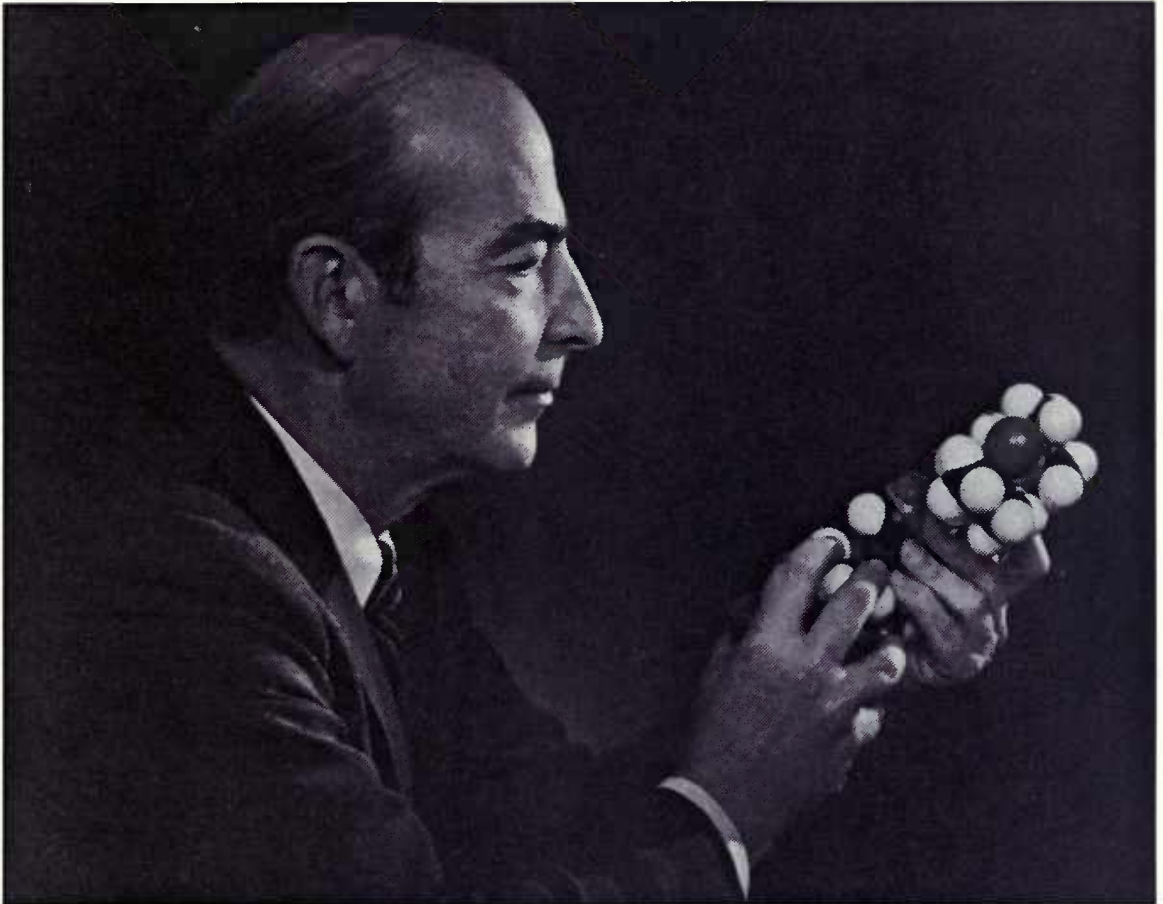
Kornberg: The highest quality of postdoc applications was in 1952, long before I was awarded the Nobel Prize. I had applications from four people for postdoctoral training that year who turned out to be world class scientists. I've never had a crop like that since.

Hughes: Do you want to name them?

Kornberg: Yes. One was Paul Berg; another was Ed Korn; another was Gordy Tomkins, who unfortunately died some years ago. Another was Bruce Ames.

Hughes: That is quite a group.

Kornberg: Yes, it was an outstanding group.



Arthur Kornberg, ca. 1965.

Photograph by Karsh

V RECOMBINANT DNA AND BIOTECHNOLOGY

Patenting in Biotechnology

Negative Influence on Academic Science

Kornberg: Is biotechnology good or bad? As I say in my book,¹ I think like any new technology, any invention, it can be some of both. But because of the enormous optimism reflected in the multi-billion dollar industry that is propelled by it, I think it is important to reflect on some of its lesser achievements, or negative influence, especially as it affects science in general and the university in particular.

The heros and heroines of this Stanford-UCSF patent [the Cohen/Boyer patents on recombinant DNA technology] have many accolades at the moment. But in the very long run, one wonders about the negative consequences of that patent, not so much the patent itself, but the whole climate that it generated here and everywhere else. In essence people thought, if Stanford could do it, why shouldn't we do it? If Stanford can get rich, why can't we get rich? If this department got rich, why can't another department get rich? So that's almost a get-rich-quick attitude that is contrary to everything that science and the university stand for, which is knowledge for its own sake, not knowledge that is lucrative.

So as a matter of policy, I think the university [Stanford] shouldn't have taken out a patent at all. Or if it was constrained by our capitalist system, that a patent would preclude others from exploiting the discovery to their benefit and to the exclusion of the university, then those patent

¹ The Golden Helix: Inside Biotech Ventures. Sausalito, CA: University Science Books, 1995. Hereafter, Helix.

royalties should have been distributed in some very general way to promote science.

Hughes: Did you express this opinion at the time?

Kornberg: Not really, but Paul Berg¹ was very active in this, and that may be recorded in some of his correspondence.

When the money was distributed that came with the patent, I was resentful that the biochemistry department, which had contributed, I would say, a major fraction of the technology and the wherewithal for the Cohen/Boyer recombinant DNA experiments, was excluded completely from any financial benefit. In this less than ideal world we scrounge for funds, and it seemed unfair that the fellowships and all of the other advantages of having this money were to accrue to departments that had very little to do with Cohen's research. I hope that my comments are not interpreted as a conflict of interest or sour grapes.

Secrecy in Industry

Kornberg: But then there is another feature of patenting--secrecy. As I've said in my book and others places, secrecy is corrosive. It results in restraints upon giving information that you as a scientist are in good conscience required to provide. It's bad if you have something that is publishable by current standards, and you withhold it for a couple of years because of a collaborative agreement with a company, or because it might affect the patentability of something that you are doing for the university, or because it might give an unfair commercial advantage to someone.

Hughes: Have you personally encountered such incidents?

Kornberg: Not in my own group and not immediately around me. But I know they exist, because such arrangements are known to prevail. They have been disclosed as part of contractual agreements between the Scripps Institute and Columbia University and their respective industrial partners. One would have to investigate further, but I am confident that there are numerous examples.

¹ See Berg's oral history in the Program in the History of the Biological Sciences and Biotechnology Oral History Series. Hereafter, The Bancroft Library Series.

Secrecy is almost taken for granted in industry. It seems like a no-brainer that if you've expended your resources to get some intellectual property produced, you are not going to share it freely with your competitors.

And yet that is wrong in most areas of science. I'm not speaking of details of some machine or formula for Coca-Cola or whatnot; I'm speaking of knowledge about a biological system that will have relevance to disease processes. And since virtually all information, 95 percent of it, comes from academia, you are so much better off as an industrial enterprise in sharing that information, getting some kind of input or criticism from others to help determine whether to proceed with the really expensive development of the discovery.

Decisions Regarding Product Development

Kornberg: I've had enough exposure to the pharmaceutical and biotechnology industries to know that discoveries are relatively common. What is most important is the judgment as to which of them to pursue, and that is a decision of dollars and cents.

Let's say for the moment that a discovery of some significance costs a hundred thousand dollars; further studies on animals and toxicity will cost several million dollars. Beyond these early tests, and going to phase I, II, and III clinical trials, we are talking about tens of millions of dollars. To get a drug approved by the FDA may take ten years and \$300 million. There are so many hurdles and marketing matters along the way. A great discovery may go through clinical trials only to be preempted by something else that is more marketable.

At the early stages you have to gauge, by clinical hurdles and marketability, whether a huge investment of money and effort is to be made in discovering A, B, C, or D. There are issues of product efficacy, safety, marketability. Those are the areas where shrewd judgments have to be made, rather than at the early stage where discoveries can be judged by a free flow of information.

I would like to see contractual arrangements between scientist and employer, or company A with company B, in which it is stated that worthwhile discoveries will be promptly and properly published; that information will be shared with other

scientists and academia and industry. I've never seen that; I don't think you ever will, because it is so contrary to human nature.

Secrecy in Academia

Kornberg: Then I go on to say in my book that it actually is more hazardous to share information in academia than in industry because if you've made a discovery in an academic institution, marketability and all the other commercial aspects don't matter. A discovery is judged on the basis of what progress it represents in solving some important problem. Not infrequently, that solution is based on some serendipitous, haphazard event which can be readily exploited. If an academic scientist were to share information regarding the optimal pH, the source of material, the temperature, the medium in which that test was done, then a half dozen others can do the same thing, and hearing about it might even publish it first. It is a real risk. Your claim to fame, if the discovery turns out to be very important, may be muddied by someone who has acquired that information by hearing it at a meeting or through colleagues and reports it at the same time or even earlier than you. So the need for secrecy in academia might seem greater than in industry.

But secrecy in academia is not the issue here. Everyone agrees that it should be avoided, so we don't need to argue the problem. But in industry, to repeat, it makes even less sense than in academia and is just as corrosive.

Commercial Applications of Biology

Kornberg: Biotechnology, by the very fact of its name, links biology to technology. Its origins were entirely academic. It has involved biologists in an entrepreneurial sense that is utterly unprecedented. The entrepreneurial eagerness of biologists was never imagined, and now impinges on some of the very basic issues of behavior in biologic science. Were there any reasons for secrecy in academia, they are now enhanced by contractual agreements. Also, not infrequently biologists enter these entrepreneurial areas because they see them as avenues for personal wealth and prestige. Even if they don't start a new business, which is rather common, they are extolled within the

university for having been the source of a patent that gave the university income and prestige.

What happens then? You make a discovery and it is in the nature of science that you increase the perimeter of your ignorance. So immediately you ask, how did that happen? If it is an enzyme, what are the genes responsible for it? How does that enzyme interact with other aspects of a complex network of reactions to which it is related? If it occurs in E. coli, are comparable genes to be found in eukarotic systems--yeast, mouse, human? There is no lack of problems that confront you when you have made a discovery, aside from verifying it. But now people think instead whether they can start a business with the discovery, thinking immediately, within the university, of exploiting the discovery for profit.

A common excuse is: "Well, that discovery will be meaningless for human welfare unless it is developed on a proper scale and tested as only industry can do. And so if this new compound which may cure diabetes remains an academic item, we are depriving the sources of our support, the public, of the proper application of this fundamental knowledge." So quite aside from its immediate commercial advantage and the greed of getting rich, you can cloak it or maybe substantiate it as a proper venture by saying, someone has to apply this knowledge, which only a pharmaceutical company can do. A small biotech venture can develop a discovery up to a certain stage, and then it must affiliate with a big pharmaceutical company for its further development.

Hughes: Do you support that argument?

Kornberg: Yes. It is the basis for biotechnology ventures.

Hughes: And you support that as a valid reason.

Kornberg: Completely valid. The university doesn't have the resources and the attitude to develop new drugs and new devices. That is really one of the great achievements of biotechnology ventures. And this in turn has stimulated the pharmaceutical companies to adopt the procedures, techniques, and attitudes of biotechnology. As you know, the big companies have been gobbling up the small biotech companies as they find them suitable; biotech ventures are desperate for funds and resources to stay alive.

Hughes: Do you yourself hold patents?

Kornberg: One I think, but reluctantly. That is one of the cons of biotechnology. Unlike chemists, it was not part of our biologic science culture to take out patents. Having found the gene for the enzyme that makes polyphosphate, I must behave within the context of academia and my university responsibilities to inform the Stanford Office of Technology Licensing. We must be concerned that this discovery might be appropriated in some legal or unethical way by somebody else and some company. It could turn out to be very profitable. The simplest thing to do is to call the Office and say, "We intend to publish this paper. Look at it and decide whether it is worth the effort and expense to patent it. I'll help you with framing the patent."

Hughes: I interviewed Niels Reimers who orchestrated the licensing of the Cohen-Boyer patents,¹ and one of the points that he made was that he never argued for holding up publication in order to file a patent.

Kornberg: I believe in the U.S., you have a year's grace after the discovery to file a patent application. In Europe I think there is no such grace period.

Hughes: Are you aware of a scientific publication being held up in order to file a patent application?

Kornberg: At Stanford, I am not aware of that. Now I think the initiative is coming from the investigator, rather than the university administration. I am not aware that publications have been held up for patent reasons.

Recombinant DNA Research

Concerns in the 1960s

Hughes: I think some tend to forget that some of the issues that were so salient in the recombinant DNA period in the mid- to late 1970s were actually voiced in science in the 1960s. I have a couple of documents that I thought might be relevant.

¹ See the oral history with Reimers in The Bancroft Library Series.

One of them is a letter that you received from Seymour Cohen in January of 1968 which proposes a meeting on genetic engineering.¹ He says:

I was very much interested in reading the account of your interview (in Science [magazine]) in which you hold up the perspective of genetic engineering with altered and carrier viral nucleic acids. You realize, I am sure, that the technology is still far from adequate, while the social and moral bases of such activities can be described at present as nothing less than frightening. I wonder if the gathering of so many nucleic acid experts (in connection also with another ACS [American Chemical Society] symposium on sugar phosphates and nucleotides) does not provide the occasion for a small one day meeting at Stanford...to explore both of these aspects, ie. the planning of the development of the technology and the problem of the conditions in which such a development should be pursued.

Do you have any recollection whether such a meeting occurred?

Kornberg: I have no recollection, let alone of the letter. And I don't recall the comments in Science that provoked Seymour's letter.

Hughes: It sounded to me as though it was provoked by your work on viral synthesis.

Kornberg: Yes, I'm sure it was.

Perhaps I was prescient in discussing genetic engineering at the time. Seymour had worked with viruses for many years, so I would take his comments very seriously. What I think he and others were concerned about eventually led to the meeting at Asilomar in 1975. (I got the date wrong in The Golden Helix.) On paper or in theory, genetic engineering was worrisome, but in terms of actual pathogenesis of a microbial or viral disease, it just didn't deserve such apprehension or the adjectives used, such as "frightening". I'm really

¹ Seymour S. Cohen to Kornberg, January 8, 1968. (Kornberg papers, SC 359, Box 26, folder: 1968 A-C.)

surprised that Seymour used that term, because he knew a lot about tobacco mosaic virus and things like that, but also some clinical virology. As an historian, I can see why you'd want to piece together incidents like that.

Hughes: Was Cohen's a representative attitude in 1968?

Kornberg: Possibly. At the time we announced the synthesis of a virus, at the Christmas season, a cartoon depicted Santa Claus homunculi emerging from my test tube. People were impressed or scared that we were producing viruses in test tubes, hairy creatures that might be overwhelming.

Hughes: Why were you so clear that it was not a danger?

Kornberg: Making a virus that infects E. coli, or even engineering something novel that infects E. coli didn't seem to me to pose any threat to people. I imagine we could modify an infectious virus to diminish the hazards in handling or being infected with it.

Most of my effort in the press conference, and afterwards, was to try to educate people as to what a virus is, that it is not a big hairy creature, but simply a strand of nucleic acid. I tried to tell people, there is no line that separates big molecules from viruses from bacteria and so on. Seymour Cohen's reaction was not general.

Asilomar and the NIH Guidelines for Research on Recombinant DNA

Kornberg: I can't recall that my work on viral synthesis created any concern or furor, unlike the commotion that was started when [Maxine] Singer and Berg declared a moratorium on recombinant DNA work until a conference could be gathered at Asilomar. When the final directives [NIH guidelines for rDNA research] emerged as a result of that conference, they were very arbitrary rules about who could do what, and they were certainly conditioned by people who had an interest in protecting Drosophila or some other creature from the perils of legislation restricting research in genetic engineering.

Hughes: Are you saying that certain scientists were interested in protecting their particular field of science from regulation?

Kornberg: Yes. And you can say in their defense that they understood it well enough to know that there was no danger. You could be less charitable and say, "My ox won't be gored. Let someone else worry." These restrictions interfered with people's immediate research plans and inhibited an enormous amount of work, which there is no way of determining, because of the cost of the P3, the P4 [physical containment levels 3 and 4] facilities.

Researchers then were constrained by new government regulations [NIH guidelines]. If you worked with certain organisms, you had to have a P3 facility. You had to have posted on the door that this was a P3 facility and a sign of "Danger." So the average person would say, "Well look, if you tell me your research is not dangerous, why do you have a big sign on the door saying that you can't enter and that it is dangerous?"

It meant that many people, laboratories, maybe even countries, couldn't engage in this work because of the impediments. To this very day it is difficult to do work of that sort in some European countries.

Scientists Opposing Recombinant DNA Research

Kornberg: In fairness, with any new scientific development, there are going to be legitimate concerns about its immediate and ultimate applications. There are going to be people who behave badly by exploiting these fears and novelties and direct attention to themselves and their own interests. Cavalieri was one, and Robert Sinsheimer behaved badly in this regard too. In the case of Bob Sinsheimer, I was angry and disturbed at the time that he was doing it, and I told him so. I felt very strongly then that it was unjustified and that it was an attack on science.

Hughes: What particular aspect of his argument did you think unjustified?

Kornberg: Well, the fear of doing recombinant DNA work.

Hughes: Wasn't his major concern that recombinant DNA technology could bridge the species barrier? That it was tampering with the evolutionary mechanism?

- Kornberg: Well, he should have known better. What is a species? A species is very difficult to define; it just means that two kinds of creatures don't breed successfully. It doesn't mean that they can't generate some hybrid that will then be able to breed and represent a great benefit or a threat. It goes on in nature all the time. As people, we breed all kinds of offspring that can be monsters; we've bred Hitlers and Stalins. So do we practice eugenics in human breeding? That hasn't worked. What Sinsheimer could have said: "Until proven otherwise, let's be cautious in handling these novel recombinants." By no means should he have confused the issue by using the prevailing concern about nuclear energy to confuse discussion of this recombinant DNA work on biologic nuclei.
- Hughes: Did you at the time have any doubt about the implications of recombinant DNA technology?
- Kornberg: Really, no. Now, you can say that perhaps I should have been more concerned. Events have proven that there was no reasonable basis for that concern.

Concern about the A-T Polymer

- Kornberg: Around 1960, we found a novel DNA-like polymer that was generated as the result of DNA polymerase action. It was called the A-T polymer in which there was an alternate succession of A's and T's. It came as an utter surprise. It took some years for us to realize that these polymers do not emerge de novo. No one had ever seen or heard of them. Once they were produced, they were very easily replicated; we had to wash our glassware scrupulously in order to remove the slightest traces of A-T polymer. Otherwise, they'd screw up the experiments. I did wonder at the time, what would happen if I infected myself with a little bit of this polymer? It could be a cancer of the worst kind. Theoretically. But the chances are exceedingly small.
- Hughes: Did you take any precautions?
- Kornberg: No, we didn't use any microbiological techniques for avoiding contamination. But it did cross my mind that this polymer that took off with such speed and abandon in a test tube might conceivably do so in a human cell. I never thought of injecting it into a cell--that might have been interesting [chuckles].

In fact, one of the startling things that no one expected is that you can create vaccines by injecting DNA; you can alter and express DNA by injecting it naked into a muscle. But it has been done often enough so that you have to believe it. What would happen if you injected this A-T polymer? I don't know what would happen. Someone ought to try it. Not on people, obviously, but in animal cell lines.

Conference on Biohazards in Cancer Research, Asilomar,
January 1973

Hughes: Dr. Berg arranged for a conference at Asilomar in January 1973 on Biohazards in Cancer Research.¹ This conference was two years earlier than the Asilomar Conference on Recombinant DNA. Do you remember?

Kornberg: I think it was well known by that time that the polio vaccine, which was grown in monkey kidney cells, contained SV40, known to be a tumor virus. If you want to write a rather attention-getting article for the Sunday newspaper, you could probably get enough material to state that the early vaccines administered forty years ago to children, now in their forties, contained a cancer virus. I don't think that anyone has shown that these people, millions of them, do or do not have any traces of SV40.

Hughes: Was that an impetus for the conference?

Kornberg: You should ask Paul why he was so concerned at the time.² But since he was using SV40 in his recombinant DNA work, it was possible then to think of modifying a known cancer virus in a way that made it more infectious.

¹ The book based on the conference is, Biohazards in Biological Research, Proceedings of a conference held at the Asilomar Conference Center, Pacific Grove, California, January 22-24, 1973, A. Hellman, M. N. Oxman, and R. Pollack, eds., Cold Spring Harbor Laboratory, 1973.

² See the oral history with Paul Berg in The Bancroft Library Series.

The Moratorium

- Hughes: As you well know, he stopped his research with SV40 for a time. How closely were you in touch at that time with his thinking?
- Kornberg: If I was, I can't recall.
- Hughes: Do you remember hearing any talk about the proposed moratorium?
- Kornberg: Yes. I was not intimately involved.
- Hughes: You don't remember him asking you for advice?
- Kornberg: No. But you know I didn't remember this Seymour Cohen letter either. My recollection of these events is very selective. As a historian you must know that.
- Hughes: Yes. How much did you know at the time about what was happening in Berg's group and Kaiser's group?
- Kornberg: A great deal. The department was small and had a tradition of sharing information. There were regular reports, both formal in the way of seminars, and in chance conversations. I was quite well aware of what was going on. Most of the students were involved, and they gave reports. I can't tell you on these specific issues that we met and discussed them, but it couldn't have been avoided in discussion.

Potential for Scientific Research

- Hughes: You had said in a previous interview, and you say it also in Enzymes, that you didn't initially appreciate the commercial applications of recombinant DNA technology. But did you and others immediately recognize the scientific breakthrough that being able to manipulate DNA in a controlled manner meant for research?
- Kornberg: I think it is fair to say we didn't anticipate the commercial applications. A lot developed from technologies. The magic technique is PCR. We didn't know then how to amplify DNA sequences. PCR requires the sequencing procedures. That was not available in the early 1970s. PCR requires synthetic procedures to make decent amounts of primers--utterly unavailable in the early 1970s. One might predict that such procedures might become available, but not in any specific time

frame. That we'd learn more about the arrangement of genes and nucleotides within genes, having manipulated phi X DNA, was a possibility or likelihood of being able to do as much for complex genomes. That doesn't take any leap of imagination. But the time scale and impact on our immediate work was really not anticipated. I can't be more explicit about this than to relate the Lobban story. [see below]

I'm going to give a talk at the International Congress of Biochemistry to be held in San Francisco. It is a triennial affair, and they asked me to give the opening talk. I've entitled it, "A centenary of the birth of modern biochemistry." In 1897, Eduard Buchner accidentally discovered that yeast juice could carry out a phenomenal biological event called alcoholic fermentation--turning sucrose into ethanol. I regard that as the signal event that led to the enzymology that resolved such events and then to their reconstitution. It was the classical tradition of enzymology that led me to DNA polymerase and DNA ligase and the other reagents without which there would be no recombinant DNA.

Others trace the history of genetic engineering and recombinant DNA from their own vantage points. If you read Horace Judson's The Eighth Day of Creation,¹ which I've only scanned, you would find a different interpretation. That's why we have many historians writing countless books about Lincoln or Darwin. Everyone has some seemingly novel interpretation to give to a life and its consequences.

Do you know one of my heroes? [points to picture on wall]

Hughes: F. G. Hopkins.

Kornberg: Good for you. I've met biochemists from Cambridge University who have never heard of him. Well, he said, to quote him accurately, [pause while he seeks quotation in For the Love of Enzymes.] "[The biochemist's] may not be the last word in the description of life, but without his help the last word will never be said."²

Along the way, in attempting to describe life and life processes, technologies are developed that then provide opportunities to do things that are unanticipated. Once you

¹ H. F. Judson. The Eighth Day of Creation: The Makers of the Revolution in Biology. New York: Simon and Schuster, 1979.

² Enzymes, p. 270.

get recombinant DNA, technologies are developed to exploit it involving sequencing and synthesis of oligonucleotides, and then PCR, all with profound effects on biology. The reductionism of enzymology goes beyond to biology itself, to create new organisms, and recently to a sheep from a single cell.

An Interview with Dr. Kornberg in 1975

- Hughes: I found transcripts of an interview conducted with you in May, 1975, only months after the Asilomar conference which was held in February.¹ I'm interested in it because it presumably reflects your thinking at the time of Asilomar. You said some interesting things. You said, you "would defend the attention given this particular scientific development"--meaning recombinant DNA technology. And you talked about "novel reproductive materials with potential for trouble," and that there was concern--I don't think you necessarily meant your own--for past and continuing "inadequate and inexpert handling of infectious materials."
- Kornberg: [reading] "On the other hand, I've been concerned about some of the dangers that arise from this kind of publicity and debate, as they're as follows: ... exaggeration of the biohazard."
- Hughes: You gave two more reasons for considering the recombinant DNA issue. One was heightened public consciousness about biohazards and environmental pollution--this was in the aftermath of the Vietnam War and the environmental movement was rolling. And the fourth reason was the increased scientific communication on this subject. Of course, you at Stanford were located at the center of such discussion; Paul Berg was one of the most, if not the most, visible figure in this debate.
- You went on to talk about dangers that you saw arise from this kind of public debate, and the first one you list is exaggeration of the biohazard. You considered fears about the technology to be exaggerated. You don't remember giving the interview?

¹ Interview with Arthur Kornberg, May 20, 1975, for the Recombinant DNA Controversy Oral History Collection, MIT. (Kornberg papers, SC 369, box 11, folder: 1978 (L-Q), p. 1.

Kornberg: No. To be honest, given the intimacy that I had with this work and the people, even if I felt concern about the excessive attention given it, I wasn't going to come out and say that it was nonsense, misdirected, or foolish.

Just as with the Human Genome Project, it has gotten around that I'm opposed to it. Well, since all my friends are involved in it, I say with sincerity but with additional emphasis, the results are very important; they are very useful. Its application will go beyond what we estimate. Then I express my concerns that this massive project with its heavy funding is taking money out of the same pocket that is needed to support young investigators. \$200 million for the Human Genome Project this year means two thousand investigators will not get \$100,000 grants. There is also the fear, which I think is justified, that once you get something like this going, it is unstoppable; you create an organization, a constituency which then remains forever, and one excuse or another will be found for it. So it is not going to vanish; there is no sunset clause for this new National Institute of the Human Genome.

I'm rambling more in this interview than in others, but I think it is one of the objects of this interview to express current philosophy and attitudes as they have been shaped or anticipated by historical events.

Controlling and Monitoring Research

Hughes: I agree. [laughter] In 1975, the department set up a biohazards committee.¹ Presumably this was an aftermath of the Asilomar conference.

Kornberg: I think it may have been a response to a directive that any research of this kind had to have such a committee.

Hughes: I think you're right. At any rate, the mandate was, "to review research projects that involve the construction and propagation of recombinant DNA molecules not presently under investigation in the department." I don't understand that.

¹ Bob Lehman to Members of the Biochemistry Department, June 2, 1975. (Kornberg papers, SC 359, box 5, folder:1974-75.)

Kornberg: I don't either.¹

Hughes: Did any of your research fall under the recombinant DNA guidelines?

Kornberg: No.

Hughes: Did the guidelines impede research in the department?

Kornberg: They may have. They certainly didn't affect mine. Dave Hogness who worked on Drosophila somehow was given immunity from these guidelines. Paul Berg's work might have been limited in some ways; he could tell you. As I've mentioned, I think we did have a P2 or P3 facility set up which took space and money.

Hughes: Set up as a result of--

Kornberg: --as a result of the Asilomar conference and the regulations and guidelines that emerged.

Hughes: Were there provisos for training in microbiological technique for those that were working with pathogenic organisms?

Kornberg: Well you know, the irony is that SV40, a tumor virus, was being handled on the open bench by people who had no credentials, no special training; they just picked up procedures from neighbors as they went along. Here was a virus that was known to cause cancer, while at the same time, some recombinant DNA constructs in organisms known to be noninfectious were under special restraints and required special facilities and other kinds of concern. It was unreasonable.

¹ The interviewer should have quoted the second paragraph of Lehman's memo: "The function of this committee is not to monitor such research once underway, but rather to review with the investigators in question the potential hazards that might be inherent in the project and to consider appropriate containment measures. Such reviews will be conducted within the framework of the report of the Asilomar Conference on Recombinant DNA molecules and any new guidelines developed by the NIH Advisory Committee on Recombinant DNA's." (Ibid.)

Potential Legislation

Hughes: Another aspect in 1977, 1978 was the threat of legislation at both the federal and the state level to regulate recombinant DNA research. I have evidence that you were directly involved.

Kornberg: I don't know how much is on the record. I know that I was involved.

Hughes: Well, I'll show you a letter that you wrote in February 1977 to Frederickson who was director of the NIH.¹ [interruption] Nineteen seventy-seven was the year when the threat of federal legislation to regulate recombinant DNA research was at its height, particularly the Kennedy bill. [Kornberg reads letter]

Kornberg: Good letter.

Hughes: Yes. I would like to read part of it into the record:

...it has become even clearer to me that what we now must fear most, is not the remote possibility of biological warfare, but instead the war on biology. If we succumb through weakness or confusion to the forces who are attacking scientific inquiry in the U.S., I am certain that the frontiers of genetic research will develop elsewhere (eg., the Soviet Union, China, Israel) and will provide a refuge for American scientists. This is a lesson from history that does not need to be learned painfully still again.²

Kornberg: It must have been about that time, and I may be off by some years before or after, that there was a visit here by Ted Kennedy, who was sponsoring legislation to control genetic research.

Hughes: That's what you were responding to.

Kornberg: And I met briefly with him. I don't remember where and exactly the occasion, but he said, "You know, this time"--referring to

¹ Kornberg to Donald S. Frederickson, February 25, 1977. (Kornberg papers, SC 359, box 3, folder: genetic engineering 1977.)

² Ibid.

nuclear energy and the atom bomb--"we want to be on the takeoff as well as the landing." And I think I said to him, because I have said it on other occasions: "Where in the takeoff of nuclear energy would you have intervened? Would you have intervened in the physics and mathematics that Lisa Meitner and Otto Hahn were engaged in exploring the nature of the atom? Would you have intervened at early stages where fission of an atom was shown to be possible and the consequences for chemistry and physics that emerged from that? If you hadn't, then it would have taken off."

We're not smart enough to know what the consequences are of new knowledge. And the worst thing you can do is to curb the acquisition of new knowledge, particularly the genetics we desperately need to know a lot more of, if we're to cope with disease and understand human development, as well as the world around us. So it is impossible to limit an inquiry--it's the worst thing you can do.

I recall a meeting with Bob Rosenzweig, who was vice president for something [Public Affairs] at the university, and a dozen or more people. Legislation had been approved by the American Society for Microbiology (30,000 members) that defined limits for genetic research and would have created a federal body to monitor this research, and probably would have required committees in every institution to conform to those regulations. I said to Rosenzweig, "It's terrible; you can't allow this." And he looked at me with some disdain, and said, "Well you don't understand what's going on in Washington. This is the best we can get." I said, "I don't care if it's the best we can get; it's terrible." And through some quirk, and again the record on this must be available somewhere, Kennedy withdrew that legislation for reasons that I don't think had anything to do with an understanding of its bad consequences--I think it was some political or parliamentary maneuver--and it died.

It is really terrible to contemplate what would have happened with creation of a federal agency; it would have gone on forever. It is natural for some groups to justify their existence by finding new problems. Take the asbestos scandal; people go to great lengths to discover some vestigial remnant of asbestos so that the industry they created to remove it can have more business. They actually create a much greater hazard in the course of removing it. [laughter] I don't think the analogy is farfetched.

The Public's Role

Hughes: Another point that Kennedy made, I believe in the same time period, was that in addition to being present at the takeoff and landing, the American public, which funds much of scientific research, should contribute to decisions about recombinant DNA research.

Kornberg: That's implied. An important point to be made is that not only would there be presumably knowledgeable scientists but also a role for the public, much as the National Academy [of Sciences] is now struggling for.

Let me digress for a moment. The National Academy (NAS) through its National Research Council (NRC) responds to governmental requests to everything that Congress needs to have information about, whether it's highway construction, childcare, teenage pregnancy, electromagnetic radiation. The NRC convenes special committees. These people have no conflict of interest; they are people drawn from all walks of life. They issue a report which is then a guide to Congress or anybody else as to what to do and not do, and what hazards to avoid and so forth. There is now a challenge from an animal rights group to have such meetings open to the public. They invoke an act of Congress that such meetings involving congressional action have to be open to the public. This will screw up all efforts to get factual information. There was a ruling just the other day by the Court of Appeals that that ruling is to stand; the NAS must either go to Congress for a new law or to the Supreme Court. Regarding the public, they include those with an ax to grind. And the ax to grind always generates fears and exaggerations of hazards.

Hughes: Is there a place for public opinion in scientific decision?

Kornberg: Ultimately the public makes its opinion known through legislation, either budgetary or some kind of regulation, and that's what we depend on in a democracy. A current campaign that I've started to get long-term support for basic bioscience research is aimed at the public, the ultimate court of opinion as to how to spend our resources. An old cliché is that you don't run a railroad democratically. But at the level of spending thirteen billion dollars a year for an NIH budget, the public has to have its input. I wouldn't rely on scientists exclusively on how to spend it.

Hughes: So you think that the process at the moment is working fairly well?

Kornberg: As is said about democracy, it's an imperfect system but better than any other that anyone has tried. The concern is that the public is ill informed and misinformed.

I read in the paper that 20 percent of the population of Austria has signed a petition against genetic engineering of foods, to permit neither the import nor the creation of them. It is so disillusioning that a civilized society can be so misinformed. If it happens there it can happen anywhere. The chefs of America decide they will not use bioengineered food. The Sierra Club came out against recombinant DNA. We had a Senator [Alan] Cranston, liberal Democrat, against recombinant DNA. I called one of his aides and was told, "I'm sorry. I agree with you but we can't reach him on this subject."

The Department's Scientific Contributions

Hughes: I found a document which expresses your argument that the recombinant work was preceded by decades of work in this department. It is a letter you wrote in August of 1977 to Paul McCloskey.¹

Kornberg: Paul McCloskey, I have to confess, is a Republican, and I don't usually vote for Republicans. But I voted for him, one of the bad mistakes I've made in political judgment, because he was running against Shirley Temple Black. But he was a vigorous guy; he was the first to propose the impeachment of Nixon. He was a congressman for many years.

Hughes: You wrote to him at his home address in Palo Alto.

Kornberg: Oh, so maybe he was retired by then.

Hughes: There is a paragraph that I want to read to you. You are replying to a paper that he sent you called, "Background on recombinant DNA research".

There was no major breakthrough at Stanford in 1973. What Stanley Cohen achieved was a significant step in an orderly trained research that can be traced accurately for at least the past 25 to 50

¹ Kornberg to McCloskey, August 8, 1977. (Kornberg papers, SC 359, box 3, folder: genetic engineering 1977.)

years. The enzymes basic to recombinant DNA research had been known for many years and their application to joining chromosomal fragments was an inevitable link in our attempt to understand the hereditary and metabolic machinery of the cell."¹

I am bringing that forward because in this "backgrounder", as McCloskey called it, he made it sound as though the Cohen-Boyer work came out of the blue.

Kornberg: Well, that is the way it is often cited in historical records of what happened in what year; it is plucked out that way. I heard Paul Berg say on several occasions, "Recombinant DNA was possible because we had access to Kornberg's refrigerator." [laughter] Meaning that they could get the enzymes and, beyond that, knowledge about how to use them. So no, I don't think that within the department there was any conflict as to the basis for that statement.

Hughes: I wasn't suggesting that.

Kornberg: No, but I'm glad that there is a paper trail that goes back at least twenty years, but it could go back further, that documents this view of the history of science.

Dispersion of the Technology

Hughes: Another thing that I wanted to document was the pervasiveness of recombinant technology in the department, and I'm sure elsewhere too, by 1982. Unfortunately, I couldn't find documentation dated earlier than this letter.² In response to an inquiry about who were the salient users of recombinant DNA technology, you said it was impossible to say because it was so pervasive. And then you list the people in your department who are using the technology, and it is almost everybody, is it not? [pause as Kornberg reads letter]

Ibid.

² Kornberg to Burt Zerner, March 2, 1982. (Kornberg papers, SC 359, box 6, folder: correspondence 1982 R-Z.)

Kornberg: Yes. By 1982, my goodness, everybody was using it. We got DNAX started in 1980 and by that time we were already stimulated by the success of Genentech, and Cetus was also involved. I'd say by 1980 it was clear that one could engineer genes and proteins, and make new drugs and vaccines and so forth. With the Cohen-Boyer work in 1973, it was evident that coli was going to be that permissive.

Hughes: As you well know, the department was a major site of the science, and also of the policy that was being developed, particularly under Dr. Berg. Do you have any comment to make about how those two areas might have interacted?

Kornberg: I haven't thought about it, Sally. At least one can say that since the science and the public policy were being conducted either by the very same people, or by people that they were in daily association with, that they must have interacted. I don't know how outspoken or vehement I might have been in questioning the concerns that were being expressed about recombinant DNA. It's already documented that I felt that they were exaggerated. There was no incident that I can think of involving any clash of personalities, any heated debates about positions that were taken. You can say, well, the family atmosphere here in the department was such that people wouldn't be highly critical.

Failure to Anticipate Commercial Applications

Kornberg: The most notable thing which I dwelt on repeatedly in this historical context is how we were unable to anticipate the wide and revolutionary applications of this technology--medically, industrially, agriculturally.

Hughes: Why do you think that was?

Kornberg: I've been writing this essay that I've referred to. I've mentioned that it was the fiftieth anniversary last year of the discovery of NMR [nuclear magnetic resonance] at Stanford. Felix Bloch was the physicist who got the Nobel Prize for that discovery. Yet I know that Bloch never imagined that the resonance of nuclei in a magnetic field (NMR) that he discovered could ever be applied to a human being to determine whether a lump in a breast was a harmless cyst or a tumor. Or that MRI (renamed from NMR) would be so refined that it would become a major tool for determining the three dimensional structure of a protein.

Another fiftieth anniversary this year is that of the transistor, which was developed at Bell Labs. Fifty years ago there was a small notice on page 20 or something of the New York Times, maybe in the patents section, on an item called the transistor. People never imagined the communications revolutions that would emerge from the transistor. Lasers were once a curiosity. Now they are used in bar codes at every supermarket, and for CDs, laser surgery, and so on. I'm saying, it is not simply that we alone were inadequate in anticipating the consequences of a discovery; it is a general phenomenon.

Industry Skepticism about Recombinant Products

- Hughes: Well, you weren't alone in this very area. For example, Roy Vagelos questioned the utility of recombinant DNA technology in drug development. Did you overlap with him at Washington University?
- Kornberg: I knew him very well, though I didn't overlap with him there.
- Hughes: He was skeptical on the grounds that he didn't think large molecules could be effective drugs.
- Kornberg: I think it's still true of him. I know that because we went to him as the president of Merck to see if he would support DNAX. There is a very strong prejudice at Merck, which exists to this day, that the best drugs are small molecules that can be taken by mouth.
- Hughes: So it was the fact that you had to inject large molecules that some saw as a deterrent to drug development based on recombinant DNA technology?
- Kornberg: Yes. Of course, insulin had been injected forever, but no one has been able to replace insulin effectively with a small molecule. Vagelos held this view long after everyone else realized that recombinant DNA and genetic engineering were powerful technologies.
- Hughes: Merck was late in getting into genetic engineering?
- Kornberg: Exceedingly late.
- Hughes: Merck did not support DNAX and other companies using recombinant DNA technology?

Kornberg: In the last half dozen years they've come around, but they were delinquent in their acceptance of this technology.

Missing the Significance of the Lobban-Kaiser and Berg Research on Recombinant DNA

Peter Lobban's Research

Kornberg: This essay which I wrote for Stanford M.D. in the winter of 1972 talks about DNA, its structure, function and size, and mentions recombination.¹ The recombination example that is given in figure 10 shows how the genes of the virus can be spliced into the chromosome of the host. It is remarkable, looking at it twenty-five years later, that although I knew about the recombinant DNA discoveries by my colleagues, the Berg group and the [Peter] Lobban-[Dale] Kaiser group, I didn't even mention this work here. I think I didn't mention it because, from what you'll see in the Lobban letter, I don't think we fully appreciated its importance. It was another feat, which much like the discovery of transistors at Bell Labs was considered by their discoverers as an advance but attracted little public notice.

Hughes: When you say you didn't recognize its importance, do you mean in terms of basic scientific research or commercial application?

Kornberg: Let me make it clear: what the Berg group and the Lobban-Kaiser group did was to take existing technology that was in place, using enzymes we could furnish them, to split the DNA and then to reunite lap joints with other DNA, and then seal them with ligase, which was discovered here and available. You take one piece of DNA and another piece of DNA, you break them, and you then through Lobban's work add sticky ends. Add A's [adenine molecules] to the end of one strand of DNA and to match them, add T's [thymine molecules] to the end of another strand of DNA. A's and T's stick together. One could have done it with G's [guanine molecules] and C's [cytosine molecules] but for a technical problem. So it was done. We didn't realize how big a deal that would prove to be.

¹ A. Kornberg. The biological revolution and future practice of medicine. Stanford M.D. 1972, 2:1:2-8.

Two years later [1974], Lobban had completed a postdoc in Toronto with a very clear vision of why recombinant DNA technology might be important. Before coming to Stanford, he had been an engineering student at MIT; he always had an engineering attitude and outlook. After completing his dissertation on gene splicing under Dale Kaiser, he went to Toronto in order to work with animal cells, because it wasn't obvious that bacteria could use recombinant DNAs to express animal genes. So he spent two years learning how to use animal cells and didn't get much done, at least it wasn't outstanding. Then he applied for jobs at twenty-two places and was granted an interview at fifteen. "Nine of those did not contact me at all after my visit," he says in this letter.¹ (The letter followed an interview I had with him as material for my book, For the Love on Enzymes, in which he is prominently mentioned.)² He got no job offers.

A key factor in the process of disillusionment that led me to abandon a career in basic research was that I found not a single person who understood the implications of being able to join DNA fragments together at will, let alone found it glamorous or even mildly interesting. If I got any reaction besides bemused silence, it typically took the form of a dismissal like, "You'll never get expression of mammalian genes in bacteria." The fact is that the scientific community was not ready for recombinant DNA technology at that point; only after it led to some significant new discoveries and had made a few people wealthy did the average molecular biologist see it in its true light. After all, the department where the pioneering work was done was slow to recognize the breakthrough it had hosted, and many opportunities were missed and skilled people allowed to drift away.³

¹ Peter [Lobban] to Arthur Kornberg, October 10, 1986. (Interviewer's copy, courtesy of Arthur Kornberg.)

² Pp. 275-281.

³ Lobban to Kornberg, October 10, 1986.

Among them, Peter Lobban, who, disillusioned by not getting any job offer from twenty-two applications, came back to Stanford to get a master's degree in electrical engineering. He now does computer science in industry.

Hughes: Did Lobban appreciate the application of his work when he was doing it in the early 1970s?

Kornberg: Well, you might interview Lobban. He is very nice, highly intelligent, and not a bitter, disillusioned person.

In my book, I said he talked in his seminars for an academic position about his recent mammalian cell work rather than the exciting recombinant DNA work.¹ He said in this letter that wasn't so: "While it is certainly true that the topic of my seminar was my postdoctoral work at most of the places I visited, it is also true that I made reprints of my JMB [Journal of Molecular Biology] paper available"--in which his work first appeared in 1973--"and spoke about my graduate work and my interest in continuing it when I had private interviews."²

Hughes: In the early 1970s, did Lobban see this technology as being significant scientifically, or did he have the vision to see that it also had industrial applications?

Kornberg: I'd assume both. It is hard to recall how you felt twelve or fourteen years earlier. But his thesis is available in the library.³ I believe, without historical research on this, that he was the first and clearest exponent of this technology and its applicability.

Cohen and Boyer's Research

Hughes: Please explain how Cohen and Boyer took it from there.

¹ Enzymes, p. 280.

² Lobban to Kornberg, October 10, 1986.

³ Peter Edward Lobban. "An enzymatic method for the end-to-end joining of DNA molecules," May 1972, dissertation #3781 1972, Lane Medical Library, Stanford.

Kornberg: That requires almost a day-by-day, play-by-play description, and I'm not as knowledgeable about that as others. You'll get a different story, of course, depending upon whom you talk to. You know about [John] Morrow, for example, a student in Paul's lab, who did experiments surreptitiously with Cohen. My book is a better source than what I'm telling you now.

In brief: it is possible that Cohen and Boyer saw the significance of recombinant DNA technology earlier than we in biochemistry did. They were working with plasmids. Stan Cohen was interested in bacterial resistance and the factors that were encoded in plasmids that made bugs resistant, because he was in the Department of Medicine and concerned with infectious disease. And so he became very knowledgeable about plasmids; he was a plasmidologist. Cohen did his work in the biochemistry department; he didn't have resources in the Department of Medicine, so he used our centrifuges. He was privy to all the developments in our department.

Boyer was interested in an enzyme encoded in plasmids which could cut DNA in precise places, a restriction enzyme. So the two of them got together and said, we can cut two pieces of DNA, two plasmids, let's say, one from one source and one from another. One plasmid carries the gene for resistance to penicillin and the other carries the gene for resistance to kanamycin. We put them together with the new technology developed in biochemistry, and get a host that would now have both genes, and therefore express resistance to both antibiotics. Easier said than done, because almost to that time--here we have to check the chronology--it was virtually impossible to get DNA into E. coli.

Mort Mandel's Technique

Kornberg: An unsung hero, Mort Mandel, a physicist at Stanford, became intrigued with biology and decided to drop physics. He heard a seminar on DNA that I gave in the physics department, which might have precipitated his decision to go into biology. I'm very hazy about what happened next, but I know he got a job with Lederberg, who was head of Genetics, which was physically joined to Biochemistry in the old building. Mort was doing some spectroscopic work, but he was aware that in our department, Kaiser and Hogness had learned how to get the DNA of a certain bacteriophage into E. coli, provided that the organism already had a resident helper virus. (The virus was very restricted to that particular kind of DNA.) Not only was

coli, unlike some other organisms, not permissive in taking up DNA, it was impregnable to DNA.

With the orientation Mort Mandel had collected from being close to and hearing about the work in Biochemistry, he went to Sweden for a postdoctoral to work with Bertani on phages. There, I think, he discovered a recipe for treating E. coli to make them permissive in taking up DNA. That procedure is now practiced all over the world, the favorite indoor sport of virtually every recombinant DNA laboratory. We still don't understand how this particular recipe works.

In any case, now that Cohen and Boyer had Mandel's recipe for putting these recombinant DNA plasmids in E. coli, they and John Morrow spliced a gene from Xenopus (a toad) into a plasmid and got it expressed in E. coli. As with sheep,¹ the basic science had been available going back to parthenogenesis. While Ian Wilmut did it, and others had tried and couldn't, there was nothing scientifically revolutionary about it, as everybody seems to think.

In a comparable way, animal genes are DNA and coli doesn't distinguish one DNA from another. If the gene encodes insulin, E. coli doesn't care where it came from. That perception, as indicated in Lobban's letter, was significant.

Over the years, and more so within the last five or ten, I've been asked to nominate people for prizes. On one occasion I tried very hard to present the case for Lobban. The people who asked me to nominate someone for a biotechnology award said they expected me to nominate Cohen and Boyer, and then proceeded to give the prize to Cohen and Boyer.

Bestowing Credit on Lobban

Hughes: Why don't you say expressly why you nominated Lobban.

Kornberg: I felt that he was more responsible for this technology than Cohen and Boyer were. Secondly, Cohen and Boyer had already had innumerable prizes and recognition, not to mention the patent which made them rich (Boyer extravagantly rich). And here was Lobban, utterly ignored, a great injustice.

¹ Dr. Kornberg refers to the recent reports about "Dolly", a sheep cloned from an adult cell.

- Hughes: My understanding of what Kaiser and his group were doing--
- Kornberg: Let's be more specific. Let's say, "... what Lobban was doing with Dale Kaiser who is a very eminent scientist..."
- Hughes: Paul Berg had also been doing recombinant work.
- Kornberg: At the same time, Lobban and Berg's group were exchanging information. And Lobban's thesis which outlined the way to attach sticky ends to DNA is clearly the first report on recombinant DNA technology. Of course, Lobban was aware of the enzymes that we had isolated and made available to him and helped him with their use. I say "we", I mean Bob Lehman, myself, people in our groups. Lobban had great resources. As Paul Berg said, Lobban had access to my refrigerator and got the enzymes that made his work possible. There was a very intimate exchange of information all around. Paul Berg and his group came to the problem from a different direction, as described by him and by me in my book. There were independent efforts in that sense.
- Hughes: You mean that Berg's group and Lobban went in different scientific directions, rather than that Berg was using SV40 and Lobban was using a different virus?
- Kornberg: The overall direction was the same, but Paul thought SV40 might be a good vehicle to introduce novel genes into animal cells.

Janet Mertz

- Hughes: There were others involved, Janet Mertz for one.
- Kornberg: She was a student with Paul. She and Ron Davis, who had just joined the faculty, determined that the restriction enzyme that Boyer had used (and perhaps purified) made a cut with lap joints, thus avoiding having to add sticky ends to DNA strands; the staggered cut is a sticky end. Two strands of DNA, cut by the Boyer enzyme, would overlap and could be joined.
- Hughes: So it was a refinement of the technology.
- Kornberg: Yes. That's how science progresses. The history I've given you, more detailed and accurate than what you may have seen elsewhere, gives you an awareness of that. A novel reagent that lets you do something novel.

Peter Lobban attended seminars that were given by me and my students and by Lehman's students. In our circle, the hybridization of DNA was very well known and accepted. These technologies were available, but Lobban put them together.

Hughes: Yes. Did Lobban also insert the hybridized DNA into bacteria?

Kornberg: No, he didn't do that.

Hughes: That was the step that Cohen and Boyer--

Kornberg: I'm just describing that at that time you couldn't do it, except with the Kaiser-Hogness technique, which was restricted to a certain phage DNA, providing the host had a comparable DNA. I still don't understand exactly how that happens.

Hughes: Does anybody?

Kornberg: You'll have to ask Dale Kaiser, who hasn't worked on this for twenty years but he would give you a better answer than I could. Okay, I've got that off my chest.

Summary

Hughes: May I sum up? In your view, the technological breakthrough was made by Peter Lobban, and what Cohen and Boyer did was to carry that breakthrough a bit further.

Kornberg: No, I think that's too broad and simple. The idea that you could take two pieces of unrelated DNA and splice them together was something that Peter Lobban proposed in 1969, using technology that was available. But no one had done it, much like PCR [polymerase chain reaction], for which all the techniques were available. But Kary Mullis got a patent and fame by putting together technologies that were in place and had already been done to some measure.

Peter Lobban, who as a graduate student with Dale Kaiser had not been doing that well with his thesis project on some aspect of phage lambda, made this proposal. The committee reviewing the proposal thought it a good idea and urged him to try it. He went ahead and meticulously and skillfully showed that it could be done.

At the same time, Berg and his group, for other reasons, thought that they could use the animal virus, SV40, to bring

novel genes into animal cells; let him tell the story. So there were parallel efforts and they were ongoing.

Lobban worked under the rather general direction of Dale Kaiser. Dale is a great scientist. He is primarily a geneticist but he thinks biochemically and is very sympathetic to biochemical techniques. He is very supportive of Lobban. I'm sure Dale would tell you that it was Peter Lobban who originated this work, with advice and encouragement from Kaiser. But the technology of introducing such DNA into bacteria that would then become the factories for expressing novel genes, including human genes, was possible because Mort Mandel provided a recipe, trivial but critical. And Cohen's and Boyer's skill in plasmidology made them able to use plasmids as the recombinant DNA.

My view for the historical record is that recombinant DNA technology had these origins and development. You'll get a different story, I'm sure, from each of the principals; they'll see it from their point of view--the Roshomon effect. But I think what I've told you is indisputable, if not complete. [chuckles]

Rewards and Omissions

- Kornberg: It has irked me a little, and I mention it in the book, that although recombinant DNA technology was done exclusively in this department, and the reagents and the knowledge made available to Cohen from this department, the considerable profits from the patents on recombinant DNA technology--a hundred million dollars--are divided three ways by Stanford rules: a third goes to Cohen, a third goes to the medical school, and a third goes to the Departments of Genetics and Medicine. Genetics and Medicine had nothing to do with it; it is simply that Cohen was associated with those departments. Biochemistry got nothing--very unfair.
- Hughes: Well, there is the Nobel Prize in Chemistry that was awarded to Berg [1980].
- Kornberg: Then there's the [Albert] Lasker [Basic Medical Research] Prize that was given to Kaiser and Berg [1980]. So yes, there is recognition. Cohen is very irked that Paul Berg got the Nobel Prize for recombinant DNA. I think he feels he should have shared that.

Hughes: Well, that was a possibility, was it not?

Kornberg: Certainly, and a certainty in his mind. It is comparable in a way to the Salk vaccine. [Jonas] Salk was a legend in his own time; he couldn't go anywhere except anonymously. He was the scientist of this generation, and yet he was never even admitted into the National Academy of Sciences.

Hughes: Why?

Kornberg: Because it was an engineering feat. He took existing technology to grow the polio virus and grew it on a sufficient scale and used existing techniques for inactivating the virus. He gave it rather courageously--it would have been criminal if it hadn't worked--to enough kids to establish that it worked. So did [Albert] Sabin after him. There are many such examples in science and I can't afford to be bitter because I've had more than my share of recognition.

The Pajaro Dunes Conference on Biotechnology, March 1982

Participants

Hughes: In March of 1982, Donald Kennedy, who was president of Stanford at that time, called a conference of academics and industrialists at Pajaro Dunes. Do you remember?

Kornberg: I remember, but I was not there.

Hughes: Were you invited?

Kornberg: I don't remember that I was.

Hughes: The academics that were invited seemed to have strong industrial connections, which you didn't have at that time?

Kornberg: Oh yes, DNAX had just started.

Hughes: I can tell you who went:¹ Donald Kennedy, Lawrence Crowley--

Kornberg: He was dean of the medical school.

¹ Martin Kenney. Biotechnology: The University-Industrial Complex. New Haven: Yale University Press, 1986, p. 86.

Hughes: Robert Rosenzweig, Gerald Lieberman, who was provost, Charles Yanofsky--why would he have been invited?

Kornberg: Well, so far, as you mentioned, he was the only legitimate scientist in the group. Charlie was respected by Kennedy; they were colleagues in the biology department. And Charlie was doing recombinant DNA work, and was a very eminent and respected scientist.

Hughes: And Channing Robertson. That was the group that represented Stanford.

Engenics

Kornberg: Channing was in the chemical engineering department. He appreciated the prospects that biotechnology would bring to chemical engineering. We were involved in an early attempt to set up a Stanford industrial venture, Engenics. So Channing invited me, but it never got off the ground. He was an early participant in this kind of thing.

Hughes: What was the idea behind the venture?

Kornberg: To get in the act. It preceded DNAX. And there were a few such inquiries. It might have been the one where some venture capitalists invited us and after two meetings with them I was completely disillusioned. [tape interruption]

What I remember of the proposed venture is that recombinant DNA work would need to extract and purify the products of whatever gene was cloned. E. coli or other microorganisms would then be cultivated and processed, and this would be the basis for an enterprise. I don't know how the business prospectus was formulated, but it would encompass recombinant DNA, genetic engineering, microbial hosts, processing, purification, and so on--very vague. Some venture capitalists on Sand Hill Road [Palo Alto] were putting it together, and it was clear that they expected it to be a profitable or marketable enterprise within two of three years. I was a little put off by them and their attitude.

Hughes: Why didn't Engenics take off?

Kornberg: I know I was disaffected, and it may have gotten a poor response from Yanofsky. I don't remember why it collapsed, and maybe it didn't collapse but was eclipsed by DNAX. DNAX was

such a refreshingly different kind of venture because [Alejandro] Zaffaroni, a close friend, has a genius for developing an enterprise and recruiting people, knowing that ultimately they would be coopted by the environment and the overall purpose in a very benign way.

ALZA Corporation

Hughes: Dr. Kornberg, in 1968 you agreed to serve on the scientific advisory board of ALZA, which I believe was your first formal association with industry. What prompted you to create that liaison?

Kornberg: It was due almost entirely to Alex Zaffaroni. Our friendship was very firm, and I admired his inventive genius and his entrepreneurial skills. I had been aware of the latter from his exploits with Syntex.

Before that, my contacts with industry had been transient and disappointing. I had visited pharmaceutical companies to give a seminar or consult for a day, and found them disheartening in that the level of science and the goals that were evident seemed ill-formed and unattainable. For example, a few people of mediocre talent would be trying to answer basic questions about diabetes or hypertension or some other serious disease. They were really largely occupied with getting a product that would protect a patent or be able to circumvent a patent. It was very commercial, very practical in a business sense, and scientifically uninspiring.

What Zaffaroni intended to do I knew from my medical training was very novel, that is, to deliver drugs in a programmed way to the place where they would be most effective, and to measure that delivery in very sophisticated chemical terms, exploring the physiologic as well as the chemical components. So I felt persuaded to join that fledgling enterprise at that time [1968], and also to be in the company of other people on the scientific advisory board¹ whom Alex had identified and I helped recruit.

It turned out to be a very stimulating, instructive, rewarding experience, although I felt that my contributions to that board--which could have exploited my knowledge of membrane

¹ Judah Folkman, Harry Eagle, and Paul Flory.

biochemistry--were really rather minimal. Nevertheless, in the sense that it led later to my more serious and sustained involvements in the pharmaceutical industry and biotechnology, it was a very worthwhile introduction. I learned things about the large-scale enterprise of the pharmaceutical industry that I hadn't appreciated before. And in the case of two failures at ALZA, I realized how important marketing is for the proper testing and ultimate utility of a drug.

Hughes: Had Zaffaroni invited you to become a scientific advisor because of your knowledge of membrane biochemistry?

Kornberg: I don't know. Zaffaroni's choice of people sometimes baffles me. It is a mixture of friendship, personal attributes, and scientific expertise.

Hughes: I know, of course, that he has founded a number of companies. Do you think he uses each experience to build upon?

Kornberg: Oh yes, he has a great capacity to learn.

His most outstanding gift--there are several--is to inspire people to contribute and sustain their enthusiasm and expertise, and to create an environment where people help each other rather than compete with each other. We can go on at some length on that score, but that's part of his genius.

On the other hand, he sees applications of science in a very novel and effective way, and in addition to this capacity to engage and to retain people in the enterprise, he is also very shrewd in financing the enterprise. Despite the ups and downs of ALZA and a number of very disgruntled shareholders, everything he touches people assume will turn to gold, and so any venture he starts is oversubscribed.

Hughes: I remember, in going through your correspondence, a letter dated 1961 or 1962, which was an invitation from Dr. Zaffaroni for you and your wife to come to Syntex when it was still in Mexico.

Kornberg: Oh yes, that was the origin of our friendship. He and his wife hosted us. I found him very engaging and I reassured him that the contemplated shift in Syntex research and pharmaceutical operations to Palo Alto would be a very desirable thing.

Hughes: Why did he ask you to come to Mexico?

Kornberg: I don't know. I think it was catalyzed by Carl Djerassi, who is a major mover in Syntex and had just come to Stanford.¹ We knew each other socially after his arrival, and also I'm sure he was aware of the biochemistry that I was involved with.

DNAX Institute of Molecular and Cellular Biology as a Free-standing Company

Foreseeing Commercial Applications of Molecular Biology

Hughes: You said in The Golden Helix², and you didn't expand, that Zaffaroni and others saw industrial potential for developments in molecular biology in the 1960s and 1970s. What did they foresee?

Kornberg: 1960s?

Hughes: Yes, it was the early date that surprised me.

Kornberg: Well, we kept in close touch, and you pointed out that I had used the term genetic engineering as early as 1968. So I am sure we talked about it. Certainly in the 1970s with recombinant DNA and the possibility of DNAs being expressed in various hosts like E. coli, his first thought was, what can you do with it? And that was probably my last thought.

Hughes: [laughs] Yes.

Kornberg: I kept saying, and recall writing, that commercial application of recombinant DNA technology was premature. And that's a fundamental difference between us, because he and a few others have that bent, to see the applicability of knowledge to some product, to some device. And I don't think along those lines. He's great at that. And that's the origin of DNAX, as you know.

¹ For more on Syntex, see the autobiography by one of its founders: Carl Djerassi. The Pill, The Pygmy, and Degas' Horse: The Autobiography of Carl Djerassi. Basic Books, 1992.

² p. 2.

Foundation

Hughes: I know you have touched upon this in Helix, but in order to have any structure here we have to get the basic elements down. Could you repeat why Zaffaroni wanted to form yet another company, namely DNAX?

Kornberg: Zaffaroni had the vision that this technology would be very important. I don't know if he ever articulated how it would be important, but he just had a sense that things could be done. What he was thinking of at the time that we put things together was to re-engineer antibodies. And I imagine it went beyond that as well.

What precipitated the origin of DNAX was an invitation Alex had from the Genetics Institute that wanted him to direct it. As I recall it, on one occasion, October of 1980, when he broached this--and I knew some of the people involved in the Genetics Institute in Boston--I said, "Well, why do you want to go to Boston and work with people who are really not that attractive. You could do it here." He said, "Well, that's what I've been waiting to hear from you for some years." And then I decided, with his encouragement, to invite Berg and Yanofsky to join as founders of DNAX.

Hughes: And that was October 1980.

Kornberg: You recall from other things I've said or written that there were overtures to each of us, Berg, Yanofsky and myself, to be involved in ventures, and we found them unattractive; they were simply profit-seeking ventures that were so alien to anything that I was doing or could imagine being successful at.

Hughes: These were all biotech ventures?

Kornberg: Yes.

Hughes: In 1980, there weren't many, were there?

Kornberg: No. They were being contemplated and organized by venture capitalists. And there was one that had Stanford involvement. The person who would know more about it and their subsequent fate is Channing Robertson in Chemical Engineering.

Hughes: Did he indeed found a company?

Kornberg: I don't know what happened. I don't think there is such an enterprise that has a Stanford connection, because we would

have heard of it. But now there are hundreds of such enterprises in the Bay Area. Every time someone gets an idea, he starts a company. [laughter]

Goals and Policy

Hughes: Did knowing of endeavors being created along lines that you didn't find terribly appealing shape how you jointly conceived of this new company?

Kornberg: I'm sure it did. Why Alex Zaffaroni is so successful is in part by his own convictions about what is right, and what is feasible, and what goals to set; and in part by coopting the ideals of those whom he has selected as partners in a venture. I don't think Alex has the same passion to acquire knowledge for its own sake that I do; I wouldn't expect him to. On the other hand, he would understand my wish to do so, and be very supportive of it.

Hughes: Do you see yourself as being largely responsible for the academic aspect of DNAX?

Kornberg: I would say that the three of us, Yanofsky, Berg, and myself, share these convictions, and they may complement each other to some extent, but in all these years, there has been no lack of such cohesion. [phone interruption]

Knowledge for its own sake is not the ideal recipe for a business, so it has to be leavened--or unleavened--with the practical reality of getting a product, and a profitable marketable product. And that's where Alex has a marvelous touch. He will not accept something that is profitable through gimmickry or outright copying of something that is profitable. So in the annals of technology, it has to be a genuine application of basic technology. In the case of DNAX, it has to be an important protein that meets all the standards and does something novel.

Attempts to Raise Funds

Hughes: You went on a fundraising trip to Japan and elsewhere. Why didn't it go well?

Kornberg: I don't know. I can imagine that there were a number of reasons. One, that we didn't have that much to offer. We just had a number of names and the beginnings of a laboratory; there was nothing underway. It was more the hope, the promise that we would do something. Second, in Japan at that time, this kind of venture was completely novel, and the pharmaceutical companies that we appealed to were even more backward than the American companies. So there wasn't any individual whose interest we sparked, and such an individual might have had very little influence on the major companies that we talked to. So we were given polite hearings but they weren't going to invest in this fly-by-night organization, even though the reputation of the people who were associated with it was very substantial --my reputation, Zaffaroni's, and other people's identified on the board.

Hughes: You and your laboratory were certainly not an unknown entity in Japan. You have had a number of Japanese scientists in your research group.

Kornberg: We enjoyed an international reputation for having been outstanding in the biochemical sciences and for the innovation of genetic engineering.

I just read in the current issue of Science that Japan has as a national commitment a major increase in the support of science. And the companies we went to were even less disposed to support something novel in science than the government itself.

In Europe, we had some doors opened for us but we didn't get very far with it. So I was very disappointed. I hadn't ever been turned down for grant applications. Zaffaroni said, "Well, before we could save ALZA, we talked to fifty-three companies."

Hughes: So being turned down was nothing new to him.

Recruiting Staff

Hughes: In those early phases and later when Schering-Plough became a part of the picture, how involved were you in finding and then consulting with the scientists that were brought in to DNAX over the years?

Kornberg: I, and I would speak for Berg and Yanofsky, was not directly involved in the advising and management of scientific activities at DNAX, to the extent or in the way in which we were in our own laboratories here at Stanford. Our chief contributions have been to recruit people with the conviction that to our mind our success with DNAX would be to sustain the best science, provide the best resources in an open atmosphere, and that the scientific viability of anybody recruited at DNAX would be guaranteed by virtue of this atmosphere. They'd have the finest resources, excellent colleagues, and publish freely.

It may have seemed like a brash promise initially, but then it was fulfilled time and again. So not only could we recruit excellent people but we could keep them in the face of competitive offers, until a job came along that they couldn't refuse. The most crucial thing that any leadership or governance of an organization can provide is to get the best people, and keep them.

Hughes: Do you remember encountering hesitation from the scientists you approached at the very idea of moving into industry?

Kornberg: Oh, yes. It was much less acceptable--certainly less fashionable--in 1981 than today. Now when we recruit people to replace those who have left, we get some of the finest applications, including people who want to leave very established positions in academia. But to this day, we, the founders, contribute significantly to recruitment of the best people.

Hughes: Did the first recruits come with the idea of spending a few years at DNAX and then moving back to academia?

Kornberg: I'm a firm believer in the unpredictability of any job or situation. All I can say is, "Look, I can't see beyond five years, but within that length of time, I'll do my utmost to make sure that it is a good scientific environment." I think that promise has been fulfilled. The other ingredient for success, and maybe I shouldn't rate it as being far behind the first, is rapport with top management at Schering-Plough. It mattered that [Robert P.] Luciano [CEO] had confidence in us and equally so with [Hugh] D'Andrade [executive vice president], and through them, the others. We're good friends and trust each other. And so if there is some rough spot in the road or something worrisome comes up, I think there is a sense of mutual respect that we ought to listen to each other and work something out rather than have it be a confrontation.

This spring there was a sense by some people at DNAX that we were veering off our commitment to do the best science and were being over-influenced by the commercial needs of Schering-Plough. So we said, "Let's devote a policy board meeting to that issue." And I think we were either reassured or persuaded to some extent by the top management of Schering-Plough that DNAX would stay on its course. The board then could convey the sense of that meeting to other Schering-Plough and DNAX people, either some of those that raised the issue in the first place, or those that had heard it. I think that has reassured people. DNAX is still a very attractive place to do science.

Initial Focus on Antibodies

Hughes: I found a press release dated March 9, 1981, which announces that DNAX intended to "combine three technologies to develop new products: genetic engineering, immunobiology, and drug delivery systems."¹ How did the original intended focus on antibodies arise?

Kornberg: As the scientific advisors and organizers, we were familiar with proteins. Most of the proteins whose genes could be cloned had already been thought of and preempted by Biogen, Genentech, Cetus, Amgen, and others. Antibodies hadn't yet been identified as potential commercial products. They were part of the immunology operation that seemed to have enormous vistas. Once you mentioned that, Zaffaroni could see medical and industrial applications of antibodies.

I recall that when we went on the trip to Japan to solicit money for the support of DNAX, I said, "Alex, I'll bet that within a couple of years when DNAX is underway, we'll be doing something entirely different than working on antibodies." We had this rehearsed dog and pony show in which Ed Haber, who was a very important medical and scientific figure in antibodies, and Zaffaroni and I made our presentations.

Hughes: Why did you make that prediction?

¹ Untitled press release announcing formation of DNAX, March 9, 1981. ("Helix" carton, document collection in Kornberg's laboratory, Department of Biochemistry, Stanford University Medical School. Hereafter, DNAX papers.)

Kornberg: Well, I thought that because the potential for doing a variety of things with this technology was so vast, and because it's so common when you start a project that you run into severe obstacles, or something else appears that seems so much more promising, that this would apply to DNAX. And we were recruiting people who didn't know anything about antibodies; we were recruiting them because they were very able people-- including Gerard Zurowsky, who worked on photosynthesis.

To digress for a moment, Zurowsky, although working on photosynthesis, was attractive because he was a very able scientist. Zaffaroni did the interviewing. (We'd nominate someone to be recruited and they'd go to Zaffaroni and get inspired.) He said to Zurowsky, "Sure, if you want to do photosynthesis, do photosynthesis." [laughter] It couldn't be more remote from anything that DNAX would want to do or Schering-Plough ultimately would want to support. Zaffaroni had the conviction that when you start doing something, people will aggregate around it; unless people are antisocial, they will discover that their interests are best served by being part of the group, which is what happened. Now Zurowsky, fifteen years later, is the most product-oriented person at DNAX.

Hughes: And he indeed worked on photosynthesis?

Kornberg: For a while, yes. In fact, for several years he kept publishing on photosynthesis.

So antibodies were attractive because it was reasonable to expect that you could engineer and improve them, produce them in quantity, and they would have not only medical applications but also industrial applications. So that's why they were chosen.

I don't know if Zaffaroni would remember or give an honest answer about his idea for a drug delivery system. But since DNAX in a sense was an offshoot of ALZA--because Alex was ALZA --we would now have exclusive access to ALZA delivery systems. To this day, ALZA hasn't developed a successful protein delivery system. Certainly, during the five years in which this contract was written, nothing even approached the point where ALZA technology was applicable. But ALZA got 20 percent of the ownership of that enterprise.

Hughes: Which it lost when Schering-Plough came in?

Kornberg: No. It got 20 percent; it got five million dollars as a gift, which was not trivial in those days.

DNAX and Schering-Plough

Marketing Issues

Kornberg: You asked who was responsible for adhering to a line that DNAX should focus on doing the best science and discover things that are of basic importance rather than mimic something else that's going on. I think we all agreed that Zaffaroni would accept the conviction we had, and in subtle ways shape it to make sure it was suitable for an enterprise that was supported by a company whose motive is almost exclusively to make a profit.¹ I don't want to say that it is necessarily as grubby as I make it sound. I'm sure Schering-Plough also has a reputation to sustain and wants to have products that are very meaningful, not another Tylenol or Bayer aspirin. Although, I don't know any pharmaceutical company which would be above it.

Hughes: If they thought they could make a profit.

Kornberg: I've had a number of discussions or arguments on this issue with Hugh D'Andrade, who is executive vice president in charge of administration at Schering-Plough and of whom I am very fond and admiring: is Tylenol fraudulent in its claims? I believe it is, and he says, "No way." You know the issue: its a drug that has been known for a hundred years, whose properties have been described for fifty years; and the makers of Tylenol simply gave it another name. Acetaminophen was known by fifty-eight different names before Tylenol came along. And then they say, Extra Strength Tylenol, when there is simply half again as much in the tablet. Is that legitimate? Well, Schering-Plough would do the same.

Somehow, that hasn't come up in DNAX because it is very nicely insulated from those marketing problems. The operation of DNAX has really been--I wouldn't say "pure"--but there hasn't been any adulteration by the need to do something that will produce a profitable entity within any fixed length of time. I attribute that to an enlightened, wise leadership at Schering-Plough, in which people who didn't have to have that sensitivity realized that drug development is a long-term operation, unlike that of the venture capitalists on Sand Hill Road. Schering-Plough had confidence in us--myself and Berg and Yanofsky--that we appreciated the long-range need for Schering-Plough to have a competitive product and that we could

¹ In 1982, the pharmaceutical company Schering-Plough bought DNAX.

collect and retain the best scientific talent. Because these people trusted me and Berg and Yanofsky. And that holds to this very day.

Hughes: Did Schering-Plough initially negotiate with DNAX with an appreciation that it would be years between discovery and product?

Kornberg: I think so. And I can quote Luciano on some occasion saying it might take ten years. They knew the history of scientific discovery and its application. They knew for example that they and Merck and other companies were investing hundreds of millions of dollars every year, and they weren't getting anything for it. So here for a very modest investment, they were entering a new technology with very able people, leaders in the field. It was a gamble, but they knew it would pay off.

Schering-Plough's Previous Ventures in Biotechnology

Hughes: Was it new for a pharmaceutical house to support a basic science enterprise?

Kornberg: Relatively so. You'd have to quantitate the degree to which they separated themselves from the management and ongoing operations. In the Golden Helix, I cite an arrangement with an organic chemistry group in Cambridge, Massachusetts. Top management at Schering had a friendship and an association with an organic chemist who set up a unit in Cambridge, Massachusetts, that was wholly supported by Schering, and nothing came of it; it deteriorated for personal and other reasons. So they could have been burned by that. But there was new management at Schering. [Richard] Kogan, who is now CEO of Schering, said, "Well, we expected you guys at DNAX to take the money and disappear after a few years." That didn't happen.

Hughes: Another venture they had just come out of was their association with Biogen. Because of their bad experience with Biogen, they could have tossed the biotech idea out the window.

Kornberg: Absolutely. On the other hand, Luciano, who was the dominant force in all of this, didn't understand biotechnology but he had the sense that it was important. When relations with Biogen deteriorated, largely for personal reasons, he wanted to find some other avenue in which to enter this field. And so DNAX came along, and the immunology business. They had

agreements for marketing drugs in France that involved some investment in immunology research, and then a task force they assembled advised them to invest in immunology. It was Zaffaroni whom they respected enormously. What mattered a great deal was the chemistry of personal interactions. In fact, one of the important people at DNAX exuded poor chemistry, and I suspect that Alex must have agreed that when this merger or marriage with Schering-Plough was consummated that that person would not be on the scene.

Hughes: So personality counts.

Kornberg: Enormously.

Debate over the Commercial Viability of Biotechnology

Hughes: I'm wondering how much Schering-Plough was influenced by the fact that pharmaceutical houses at this time were just beginning to form alliances of one sort or another with biotech companies.

Kornberg: Reluctantly. As we discussed, Roy Vagelos at Merck was resistant to it. We went to him for support of DNAX and he would have none of it.

Hughes: Why again?

Kornberg: Despite his knowing me, and being an admirer and having a healthy respect for Alex, Roy had a conviction that this field would produce only proteins which would be difficult to administer. A conviction that he holds to this very day is that small molecules taken by mouth are the way drugs should be administered. So Merck has been late and reluctant to be involved in biotechnology.

Hughes: What I'm trying to get at is the possibility that Luciano was trying to stay ahead of the competition. There are probably many reasons why he and others at Schering-Plough were interested in this alliance. But one of them could have been that he saw that some pharmaceutical houses were beginning to move in that direction. Smith-Kline by that time [1981] had started up an in-house biotech venture, and Eli Lilly was involved with UCSF.

Kornberg: Exactly. And Genentech too.

Hughes: Do you remember any talk about Schering-Plough getting on the biotechnology bandwagon quickly?

Kornberg: I think by 1981 when these negotiations started, they had a lot of exposure with Biogen; they were on the board and funded Biogen at a time when it was crucial to Biogen. So bringing in a biotech enterprise was not novel at all, and I think they had a commitment to get in on that. I don't think they were pioneers; Cetus already was in it; and Genentech had established that it was doable. No, it was not as adventurous an act on their part.

Given Schering-Plough's stature in the pharmaceutical field, which was mediocre at best--they were a second-rate company, to be generous--I think Luciano's leadership was absolutely key. He also had good strong advice from D'Andrade and maybe some support from others.

A pharmaceutical company is the most autocratic organization you can imagine, by and large. The CEO of the company is king, and as long as the company is profitable, he retains that authority. He delegates, of course, and tries to recruit and retain very able people in each field who made key contributions, but the CEO is absolutely the first and last authority. And the board of directors that he appoints--there is a nominating committee, but that's perfunctory--has a major responsibility to shareholders, but really won't interfere in operations. Of course, they are consulted on an issue like DNAX, and someone may raise a question or two, but over the years, they have never asked why Schering-Plough is investing a very substantial fraction of its budget in DNAX; Schering-Plough has been profitable every year. Also Luciano doesn't have any scientists on the board. They wouldn't know what questions to ask. [laughter]

Problems with Middle Management

Hughes: I remember reading in Helix that after a series of electrifying discoveries of cytokines and their genes at DNAX in the first few years after the acquisition, discoveries didn't continue at quite as rapid a pace. At that stage, were you aware of any hesitation by Schering-Plough about supporting an institution which was not producing products?

Kornberg: We had trouble with middle management. And that's often a problem because the middle manager, in this case, Frank

Bullock, is told, "We have to have so many discoveries that go to the FDA for approval per unit time." And so he is under the gun to produce something. He thought, These guys in California are laid back, immune to these kinds of pressures, having fun doing what they please, with no thought of having to come up within any time frame with something that is submitted to FDA, and they are consuming a significant fraction of my budget. That attitude got to a point where it was clearly annoying and even obstructive, and that's when Bullock was removed from that position of authority over DNAX.

Hughes: By Luciano?

Kornberg: By Luciano.

Hughes: Who continued to hold onto the vision that it was going to take a while to produce products, and that scientists had to be given a loose rein?

Kornberg: Luciano also had confidence in the management by Al [J. Allan] Waitz, who is a Schering-Plough person from way back and who enjoyed Luciano's trust.

Hughes: Waitz came to DNAX for a trial year as president and CEO.¹

Kornberg: Yes. And sometimes these decisions appear minor. I've tried to intervene at times when the issue is great. For example, it is conventional or maybe even unfailing that when you enter a pharmaceutical company, you get a badge; you log in, and you carry some indication of who you are and that you're a visitor. Even ALZA does that. At DNAX we'd have none of that. You could come and go as you please, anywhere. I thought that was an essential atmosphere in an academic institution, and DNAX, by its very proclamation of intent, said there were no secrets; we are open; we exchange innovations, et cetera. Then the current president, Jacques Chiller, in response to pressure from Schering-Plough for security or some other purpose, agreed that you couldn't enter DNAX by the side or back door without a passkey. You can come in the front door. There are still no badges. I objected. I thought this practice was contrary to what we'd established, but I was voted down. Little things like that, when added up or expanded, them, do erode the ambiance of a place.

I don't think Waitz would have succumbed to pressure from Schering-Plough. It's a very bureaucratic organization; it

¹ The Golden Helix, pp. 126-127.

employees 20,000 people, and each bureau and group has its own responsibilities. So the accountants, the lawyers, the security people, the real estate people have a good deal of authority; that's their job. So when DNAX is told, "Our insurance status requires that there be regulated access," it can say, "Well, not here." "Well, we gotta do it." "Well, not here; I won't let you do it." Then the issue goes to a higher authority which says, "Well, DNAX better do it." So how much do you challenge it? Well, Waitz would have challenged that.

Hughes: As we've mentioned, DNAX was discovering and cloning cytokines at a rapid rate. Were you involved in decisions related to which of those to actually follow up on?

Kornberg: No. It puzzles me to this very day that those decisions were made at Schering-Plough on a basis that I can't fully fathom. Let me elaborate on that. And it then relates to secrecy. Discoveries are made with a certain frequency, and if you calculate discoveries per unit time, per capita, or per cost, they are relatively numerous.

Just for the sake of illustration, let's say that a discovery costs a million dollars, if you figure in all the time and all the failures. Now, the decision to pick one of those cytokine (interleukin) discoveries to go to the next stage of putting it into animals and determining toxicity and effectiveness may cost ten million dollars. To take it to the next stage in which there are serious clinical trials and several hundred patients costs maybe fifty million dollars. To take it through phase three ultimate clinical trials, where you administer it to a lot of patients and then apply for approval, is estimated to cost on an average three hundred million dollars. And by that time it has taken ten to twelve years.

So the decision about what to select for development and proceed at each stage along the way is dictated by judgments that involve marketing, competitiveness with other products, the likelihood that new discoveries will be made by somebody else that will preempt this one, patent lifetime, and the other discoveries that are competitive within your pipeline. Those decisions are made at Schering-Plough. And sometimes I am surprised that they feel able to make them or at the choice that they've made.

Hughes: They don't consult with their scientific advisors?

Kornberg: Oh, there is some consultation. They're important for DNAX because if Schering-Plough has made the wrong decisions, if they've picked the wrong horses, then DNAX will be saddled with

those failures. No one will say, well, DNAX gave them a choice of five and you picked one that doesn't work. Or, even more serious, DNAX presents these discoveries and says, "Hey, this looks good," and Schering-Plough doesn't do anything about it for two or three years.

That's happened. IL-4 was an example. GM-CSF [granulocyte/macrophage cell stimulating factor] was another example. And then the competition makes the same discovery and presents uses and applications, for which they gain patent positions. If Schering-Plough hasn't exploited DNAX's discovery, DNAX suffers. That situation came up a couple of times. Jack Chiller, more so than Waitz, makes every effort to inform and advise. New organizational arrangements have been put in place which include joint committees of DNAX and Schering-Plough people for the development of some of the discoveries. They need to identify areas and questions that can be used to help understand the discovery and find the best indications for its use.

Hughes: It could be that development required new scientists with different abilities, different technological expertise. Did you find over the years that Schering-Plough, in making choices about products or discoveries to develop, was willing to follow up with the necessary resources?

Kornberg: You put your finger on a very serious problem, and that is that with DNAX having a focus on immunology, you would expect that there would be a comparable strength for development of immunologic discoveries at Schering-Plough. And it didn't exist.

Hughes: How could that be?

Kornberg: Simply because the middle management there was busy doing other things. On one occasion when I tried to intervene, I was told, "Lay off. Don't manage our New Jersey affairs; let the East be East, the West be West."

Hughes: Well then, why put effort into DNAX?

Kornberg: I'm saying that is a very serious matter. The integration of discoveries into development, even within an organization, is subject to all kinds of politics and bureaucracy. And this was one of the major difficulties in improving what went on in New Jersey. It has improved a great deal, but I am saying that the gap was serious and resulted in major losses.

- Hughes: After the first wave of discoveries, when the competition was getting stiffer--
- Kornberg: Absolutely.
- Hughes: DNAX lost at least two cloning races.¹
- Kornberg: Yes, to Immunex.
- Hughes: Do you care to explain?
- Kornberg: Yes. The atmosphere at DNAX was to make basic discoveries in immunology. They were not as focused on getting quickly to an interleukin discovery. Other ventures, like Immunex, had no objective to pursue an understanding of basic questions in immunology, but rather were gung ho and competent to clone. So they could throw twenty people at a project like that in which DNAX might have two or three. Very serious.

Expression Cloning

- Hughes: Another approach used by DNAX was recombinant DNA technology-- genetic engineering.
- Kornberg: The technology of expression cloning that was developed at Stanford in Berg's lab was perfected at DNAX. Because we had at DNAX very able young molecular biologists, very important discoveries were made of some of the interleukins. DNAX had an edge. In this field, you can enjoy an edge for a year or two, but once something is published, others have the incentive to acquire it and enlarge on it, modify it and own it.
- Hughes: What did the expression system entail?
- Kornberg: It entailed the facile copying of an RNA message into DNA, and then taking that DNA copy of the message and inserting into cells. One then looked for an effect on those cells that had not been present before the message DNA had been introduced. For example, an assay might reveal that the message made cells grow more rapidly. With that opening, you could then fractionate the DNA copies of millions of messages down to thousands of messages, then tens, and eventually down to one

¹ J. Allan Waitz to Policy Board Members, December 29, 1986. (DNAX papers, file box: DNAX 1987-88.)

message, and thus to the gene responsible for an interleukin, IL-3 or -4 or -10. DNAX was probably the first to use that technology seriously, and for maybe a couple of years enjoyed a great advantage.

To make it simpler, expression cloning enables one to isolate a certain message because the recipient cells display a certain property. And you could then clone that message by having narrowed down the population that included the "active" molecule.

Hughes: How else could it have been done at that time?

Kornberg: Well, if you already knew the actual structure of, let's say, insulin, somatostatin or growth hormone, you could directly get the gene that was responsible for it. The product of the gene, might be insulin, for example.

Hughes: The expression cloning system has the advantage that you don't have to know--

Kornberg: What the product is.

Hughes: Is DNAX's possession of that system part of the explanation of why the cloning of the interleukins 3 through 6 and 7 was done quickly?

Kornberg: Yes. Able people exploiting that technology made a big difference initially.

Interleukins

Hughes: When Schering-Plough acquired DNAX in the spring of 1982 and said it would be directed to interleukins rather than to antibodies, this was not seen as a defeat?

Kornberg: Not at all. It was welcome.

Hughes: You could look at the original agenda which was focused on antibodies and see its abandonment as a price that the founders of DNAX had to pay for Schering-Plough's commitment.

Kornberg: If there had been progress in the cloning and engineering of antibodies, and if the staff there through previous training and activity in that field was very much in the majority, then asking DNAX to do something different could have been seen as a

price to pay. That wasn't so; there had been very little progress in the antibody work; largely getting the lab organized, getting people in place, and starting to do some expression cloning. So, Schering-Plough saying, "Well, why don't we focus on T cells, which upon being activated produce a few distinctive proteins as judged by gel assay?" seemed very welcome.

Hughes: Did the existence of the Lyons [France] lab feature in your thoughts at all?

Kornberg: I think it might have figured in Schering-Plough's interests that this very alien activity might then be directed by an organization that was more able and disposed to do so. From DNAX's standpoint it didn't enter into consideration. Schering-Plough considered the Lyons operation to be a responsibility of the director of DNAX. It was a very minor operation there.

Ken-ichi and Naoko Arai

Hughes: At a November 1983 Department of Biochemistry faculty meeting, DNAX was discussed in the context of giving Ken-ichi Arai a consulting professorship. Does this indicate tacit acknowledgement of the quality of at least one of the scientists at DNAX?

Kornberg: Was he given the faculty position?

Hughes: Yes.

Kornberg: Well, it's really a trivial appointment that carries no obligation by the department. On the other hand, you don't hand out these appointments without serious concern about the desirability and the credibility of the person. Ken-ichi Arai is an extraordinary person.

Hughes: Were you involved in his recruitment?

Kornberg: Oh yes, I was directly responsible. He and his wife [Naoko Arai] had been postdocs with me. They went back to Japan. For them to accept not only an industrial job but with such a fly-by-night organization!

Hughes: Why did they?

Kornberg: Number one, even though she was a Ph.D. and M.D. and had this training with me, she had no job when she went back to Japan. Number two, he was given a very small amount of space and resources within the orbit of [Yoshito] Kaziro, his former advisor, and no opportunity to do anything novel or anything on DNA replication. It was not Kaziro's fault; he had limited resources, and that's the way he operated. So here was a means for the Arais to escape from that. She would get a very respectable position and authority, and he would have resources that were previously unavailable to him. Then there was their trust in me, that I wouldn't be recommending something to them that was different from what I said it was.

Ken-ichi became the franchise player of DNAX in his aptitude, his vision, and his energy. It rubbed some people the wrong way because in the rough and tumble of getting about and doing things, he did bruise or knock some people over, but no question that he was the driving force. He taught immunologists molecular biology; he taught himself immunology and was a bridging element within the scientific environment. Very outstanding.

Biochemistry Department Reaction to DNAX

Hughes: How did the biochemistry department react to DNAX?

Kornberg: I don't know. Since no one beside Berg and myself was involved in anything commercial, it could have been seen as worrisome; there could have been jealousy. The people here knew Ken-ichi was absolutely outstanding. He had been here for three years, so there was no doubt about him as an individual. In fact, before he went back to Japan, he had been offered academic positions in the U.S. on the strength of my recommendations and his performance, and I think he got a couple of firm offers.

In our departmental meetings, things were decided by consensus; we didn't vote on issues. If someone had serious reservations, they'd mention them and they'd be discussed. And if they were amplified by others, then we would be involved in some new action or a lack of action. I think there was reasonable apprehension that the department would be seen as allied with some venture. Did we have the Industrial Affiliates Program started by then?

Hughes: About the same time, 1980.

Kornberg: So the department wouldn't have wanted to be seen as having an exclusive or preferential involvement with one enterprise. Anyway, somehow it got done.

Hughes: You don't remember it being a subject of discussion?

Kornberg: I'm trying to say that if polled individually and secretly, there might very well have been dissension. It wasn't serious enough to upset anybody.

Debating the Association with Schering-Plough

Hughes: At the beginning of DNAX's association with Schering-Plough, do you remember having some hesitations because of your perceptions about the nature of the pharmaceutical industry?

Kornberg: Here are the elements. Number one, I think DNAX had four million dollars, and we were running through it at a fast pace. Alex Zaffaroni does things on a grand scale, and so with the style and the expense that resulted from it, we were running out of money. Where would we get more money? We had tried and hadn't been successful. Here people came along and said that they'd fund us completely, and over a number of meetings agreed that we would continue to do research in a style that we wanted done. They were 3,000 miles away and said, "Trust us."

One member of the DNAX organization, William O'Neill, Vice President for Corporate Development, thought it was a blunder. "You can't trust these guys." And so he tried to dissuade us from doing it.

I really trusted Zaffaroni enormously. If he had thought it was very uncertain or unsavory in any way, I figured he'd sense that. But at any point in those early negotiations, something on either side could have turned it off. The fact is that it was Zaffaroni who got the first four million dollars, and it wasn't obvious where the next four million would come from. Four million would only last a year or less. So those are very persuasive elements.

Hughes: Tim Mosmann, in 1988 in a long memo explaining why he was leaving, reminisced about DNAX, "The early years of Schering management had difficult moments, but after some of the 'unapproved' projects started to bear fruit, there appeared to

be much more confidence that many of the scientists were thinking along useful lines."¹

Kornberg: I don't know that there was anything that was unapproved. And I wonder why he said that.

Hughes: He doesn't elaborate.

Milestones

Kornberg: I did want to mention this: in the articles of agreement, Schering-Plough required that there be milestones met in order for Schering-Plough's stock to be distributed to DNAX shareholders. [telephone interruption] We tried to persuade them that milestones were silly; that they were straw men, and that you could set them up in any way you wish in science. "Yes, yes, yes, but we have to have milestones."

The committee to determine whether a milestone had been met consisted of Berg, Yanofsky, and myself, who would be the recipients of the stock, and a member of their board, Guy Stever, who was a physicist and really was in no position to judge. So it was clear they were following a well-established procedure and wanted to be seen as responsible in corporate procedures. Each year, it was a sort of a ritual that DNAX spelled out milestones, and at the end of the year we said, "Well, we fulfilled them." In a pharmaceutical operation, you could say, "The toxicology will be done by such a date, and at another date we'll produce enough material that fits all the criteria for purity and safety, and another date..." So there are justified milestones in industry.

Hughes: Associated with money?

Kornberg: No, the milestones are set for a group within the corporation. And then bonuses, salary increases, other things are determined by how well the milestones have been met. But milestones were utterly inappropriate for a research operation of this kind. And so they listened to me and said, "Oh well, let's set milestones anyway." And eventually they were no longer needed because the money had been paid out after four or five years-- the shares had been distributed.

¹ Tim Mosmann to J. A. Waitz, November 30, 1988. (Box: DNAX 1987-1990, Kornberg laboratory document collection.)

Hughes: There is a memo from Waitz to the policy board, dated December 1986, stating: "The past half to one year has documented that we are in a very competitive area, that we have lost two cloning races, one by a few months, to Genetics Institute and to T. Honjo..."

Kornberg: Who is a Japanese investigator.

Hughes: "...there is the strong belief that the current phase of discovery of novel lymphokines will not continue more than a few years; that now is the time to stake out a strong position in the field."

Kornberg: Yes, around 1986 DNAX no longer enjoyed any advantage in the lymphokine field. [pause while he seeks a document]

This is a statement I made at a meeting we had of the policy board this spring. You might read that. [tape interruption] I thought it should be stated that DNAX contributions went beyond discoveries that were then developed. [He summarizes his board statement:] upgrading and recruiting of Schering-Plough personnel; increased advice regarding screening assays, techniques, strategies; consultations on development and licensing; enhancing the image of Schering-Plough presence in biotechnology. If that advice had raised the stock one dollar, it would pay for DNAX several times over. Luciano told me a few years ago that they now had initiatives from people and organizations for collaborations that they never would have had before. And he attributes that to the DNAX image. These are intangibles, but--.

Hughes: But with very tangible results, in some cases.

Kornberg: Yes. And perceptive people, like Luciano and D'Andrade, know this. Then, if you compare discoveries per dollar spent at DNAX versus Schering-Plough, I think DNAX has a much better record. I mean, what is in the pipeline; what looks good; what's coming along.

Hughes: There's only one product on the market. Am I correct in that?

Kornberg: Yes, that right; and it's not a blockbuster. I don't know how profit accrues from it; it certainly doesn't pay for the DNAX budget. But IL-10 is in the pipeline; there's an IL-5 antibody; there are other things that are promising, any one of which could pay for all the investment in DNAX. It's a chancy business.

Reconciling Interests within DNAX

- Hughes: Yes. Tensions arise when entities starting from different premises come together--scientists interested in obtaining new knowledge, and business people interested in obtaining a marketable product.
- Kornberg: Or as Luciano put it: "Schering-Plough is not in business to do research; it's in research to do business." To make a profit.
- Hughes: Yes, that's what we've been talking about: how do you get these two perspectives to work together?
- Kornberg: The reason why I wrote the book is that it is a most unusual marriage. It is a most unusual in being a successful marriage. So since it is so anomalous, why try to learn anything from it? And the answer is, there are components of that marriage that could be adopted. I've had a number of good responses where someone has said, "I've bought a half-dozen copies and given it to all my managers."
- Hughes: That pleases you?
- Kornberg: Well, sure. [laughter] This head of research at Bristol-Myers Squibb said, "I'm making you rich by buying a half-dozen copies." [laughter] I'm rich in pleasure.
- Hughes: There was also tension between the molecular biology group-- this is probably the late 1980s--
- Kornberg: And the immunology group. Whenever we have two people there are going to be tensions. And then there was the Japanese group and the native group.
- Hughes: Weren't those groups pretty much the same? Weren't the molecular biologists mainly Japanese?
- Kornberg: Yes, I suppose that is true. But the tension between the immunologists and Ken-ichi was not on a language basis, because Ken-ichi's use of English was very good. There were tensions then; there are tensions now.
- Hughes: Are tensions associated with business different from those in science?
- Kornberg: Yes, in a sense. In a conventional academic department, there are a dozen professors and each one is an entity unto himself; a duchy I would call it. Professors are self-sustaining in

getting their money and in acquiring results and publishing them. One can be successful and surrounded by failures; it is possible.

DNAX is not organized that way. DNAX is an entity in which discoveries have to be fed to some other entity that then over a period of time makes products out of them, applies them in ways that are profitable to that entity. It's very good in the sense that when the discovery is made at DNAX, everyone has access to it and can build on it, advance it. That doesn't occur in any academic organization. That doesn't occur in pharmaceutical companies where there are layers of authority and bureaucracy. So to the extent that tensions and jealousies and counterproductive forces exist, it destroys the greatest asset of DNAX, its communal strengths.

Now within DNAX, there ought to be room for people pursuing something that is creative and not in the mainstream. But ultimately that activity or advance ought to be quickly understood and available to others. So it's communal in that respect, and therefore dissensions are much more serious.

At one point, DNAX had a chemical analyst who was very temperamental; half the DNAX people learned how to get long with her and use that facility, and the other half didn't. You can't tolerate that. You couldn't fire her because even within industry you have to have very good cause, and she could have sued DNAX for gender bias or something else.

In an academic department, if you have a group in which somebody doesn't get along with other people, people say: "Oh well, that's the way it is." But it is very difficult to tolerate at DNAX, and it is counterproductive to have it. The existence of DNAX and other biotech ventures of this kind is precarious because they need to be successful at some point beyond acquisition of knowledge. Even though DNAX enjoys the patronage of a very rich company, it still has in the long run to justify its existence.

Hughes: When you are recruiting new scientists, is a collaborative outlook one of the things you look at?

Kornberg: Absolutely. A very important ingredient is that the scientist would enjoy that kind of atmosphere. A reclusive, paranoid person within a group can be very destructive. I don't want to imply that willingness to collaborate isn't also valuable in academia. It is more so at DNAX, an organization of two hundred people. It is not a university laboratory group of ten or twelve people.

The Postdoctoral Program

Hughes: Would you like to comment on the postdoc program at DNAX?

Kornberg: Yes. I've written memos on that to defend it at DNAX or promote it at Xoma or other organizations. I think it's a marvelous program, and at DNAX now, some seventy people are postdocs; they outnumber the staff scientists by more than two to one.

Where shall I begin? First of all, the caliber of applicants is exceedingly high, and that's because the program has been very successful; it has been internationally recognized and sought after. These people come for a period of two or three years, and they are motivated to succeed and to become successful job applicants. About half of them go into academia and half go into industry. They bring fresh ideas and new techniques; they work very hard. Occasionally, one such person is identified as being competitive with outside people for appointment to a staff position at DNAX. And then there is the intermediate level where someone is sort of a senior postdoc for a number of years for personal reasons or the advantage of DNAX.

The bulk of the work at DNAX, maybe 90 percent, is done by the postdocs. When they leave, they become very important alumni, ambassadors, in their positions wherever they are around the world to recommend other postdocs; to provide for a very good image of DNAX. There are a variety of ways in which these now successful young investigators around the world can be of benefit to DNAX--collaborations, all kinds of things.

The only thing that can be said against the program, and this has been brought up many times, is that if you have a technical activity that you want to push very hard that is not appropriate for a postdoc, you've now committed space and financial resources that make it difficult or impossible to install such a facility. And postdocs do come and go, and so the very able people turn over. But that's a great asset because the turnover is very desirable. On the other hand, you lose some very experienced people. All in all, I think the postdoc program is exceedingly positive.

Hughes: According to your book, approximately 50 percent of the postdocs go on to an industry position and the other 50 to academia, and academia accepts the value of a postdoc at DNAX.

Kornberg: Absolutely. Ten years ago Ken-ichi kept coming to me crying that DNAX wasn't getting any postdoc applications. And I said, "Well, it takes time. You have to establish DNAX's reputation, its credibility." And with time that has happened.

Yes, there is no organization within biotech or the industrial world that has anything resembling this program. In fact, DNAX is unique in having [U.S.] State Department status for visa applications for special training.

Hughes: How did that come about?

Kornberg: I don't know, and I don't know the exact term for it. But it is a prestigious thing, and it makes it easier for foreigners to get visas and to stay here.

Hughes: In August of 1988, you wrote to Waitz of "the striking Balkanization of research goals and projects at DNAX."¹ I suppose this is an example of what you were saying, that scientists are used to having their own duchies.

Kornberg: Yes. In the IL-4 discovery, there was a lot of dissatisfaction as to who got credit for this or that, and some strong advice that people ought to veer off on separate research projects and not become that confluent.

Also in the early days of the postdoc program, it was thought that the postdoc should work on something entirely different so that it wouldn't be seen as a company project. But if that is taken too far, then it is counterproductive. I think there have been course adjustments to make communal projects more important than individual projects. Very tricky --you don't want to discourage someone from being curious about something that others aren't curious about. And so there has to be some latitude. But overall, you don't want a hundred different projects going on; that's a bad recipe too.

If the projects at DNAX are really basic and productive, why not have postdocs involved in them? It's more meaningful to them to have assays in place, techniques available, and then they'll seek creative ways in which to expand on them.

Do you know about the Hajume research awards? Each year an award is given to a postdoc who is judged to have done the most distinguished work. It originated to memorialize Hajume

¹ Kornberg to Allan Waitz, August 15, 1988. (DNAX papers, file box: DNAX 1987-88.)

Hagihara, who was a very bright young postdoc, M.D., Ph.D., who died suddenly of an asthmatic attack. Everyone was dismayed. His parents decided to endow an award in his memory, and DNAX contributed very significantly to enlarge the award. This year there were a dozen applicants and they were all excellent applications. And then we as a group, the founders and Chiller, picked the winner--very difficult. But I mention it because they were really impressive applications. I don't think anyone at Stanford can boast a group of postdoc achievements like that.

Hughes: What is the award based on?

Kornberg: The description of what they've achieved in a year or two at DNAX.

Hughes: In that same memo of August, 1988, you stated that the contributions of the scientific advisors "have been spotty and unsatisfactory to the staff as well as to themselves."¹ And yet I'm quite aware, after having going through your documents, that the prominent members of the scientific and policy advisory boards were featured as a feather in DNAX's and consequently in Schering-Plough's hat.

The Scientific and Policy Advisory Boards

Kornberg: A scientific advisory board can serve several important functions. It can give advice in special areas of its members' expertise. They are an audience to which the scientists can present their work and gain visibility because of the eminence of the board. The board, through other connections, can bring collaborations to DNAX and can help in recruiting people. This requires that the board be renewed or rearranged in the course of time with DNAX's needs and interests, and that its members be informed and, as a result of that information, be able to give advice in a proper way. That's not easy to do.

You have board members come for a day, a day and a half, get input on what is going on at DNAX in detail and also overall problems, and then give a response. If you ask them to write a response, they won't do it. So how you use the board, its composition, how you inform it, how you get feedback are tricky things. If it's managed well, it is very desirable.

¹ Ibid.

Hughes: I saw a memo from Paul Berg approving the new structure of Scientific Advisory Board Meetings.¹

Kornberg: Yes, I think at some point he worked on it. We had some very illustrious figures in immunology and cell biology repeatedly give strong endorsements of the people and achievements and overall ambiance at DNAX. That then gets fed back to Schering-Plough: here are people of great eminence who look at it and say, "Hey, this is a top-flight operation."

Hughes: I am not clear on the distinction between the Policy Board and the Scientific Advisory Board. Did they arise at a common date?

Kornberg: I think so. The Policy Board is made up of the four founders and the president of DNAX, and four people from Schering-Plough, including D'Andrade and Kogan, who is next in line to Luciano.

On the Policy Board, we inform each other of what's going on at DNAX and at Schering-Plough that is relevant to DNAX, and discuss policy. We meet four times a year. Part of the purpose is to meet socially, at dinner, and on one occasion with our wives. This has been important--crucial--for the healthy interpersonal relationships and the friendships that have been built up over the years. The Scientific Advisory Board meets once a year to go over the science at DNAX, to bring expertise from their particular places in science to bear on DNAX's problems, and to reflect on individual projects, people, and overall scientific directions at DNAX.

These functions are overlapping in the sense that there are policy issues at DNAX, and sometimes some reflection on DNAX's relationship to Schering-Plough, that these people coming from various places in academia, some with commercial connections, can offer advice or see problems. Could DNAX get along without a scientific advisory board? Yes. Could it get along without a policy board? I'd say no, because that bridge and the personal interactions are essential.

Hughes: Does the Policy Board consider how to follow up on a discovery? Is that the sort of issue that it deliberates?

Kornberg: Yes. Although you'd hope that with a board that meets so infrequently--four times a year and for a brief time--that

¹ Paul Berg to Kornberg, January 31, 1989. (DNAX papers, file box: DNAX 1987-1988.)

issues would be resolved outside it and either reported on or confirmed at that meeting.

Hughes: Several of your top scientists left in the early nineties, Ken-ichi Arai being one, and--

Kornberg: Tim Mosmann and others.

Hughes: Was that a worry?

Kornberg: Well, it was worry--would we be able to replace them with people of equal talent? And the answer is we did. On the whole, I think the replacements--younger people--have given us fresh points of view and talent. So I think we've done well.

Restrictions and Patents

Hughes: Was it a given that procedures would be made widely available, that they would not be proprietary?

Kornberg: Well, it's a tricky thing. Even in academia, people are secretive about something they are doing that would permit a competitor to overtake them. As an illustration, we talked about expression cloning that had been developed here in Paul Berg's lab. Well, very soon after it was practiced at DNAX, people from Stanford would come over to DNAX to learn how to do it. I don't know that there is any strict accounting, but DNAX has given out more reagents and procedures than it has acquired.

Hughes: With any strings?

Kornberg: I don't think there have been any strings. Now, if you have a new interleukin, you don't want to put it in the hands of some clown who will misuse it and then publish that it's very toxic or ineffective; there has to be some control over the use of a reagent. Yes, there are some reasonable restrictions that anyone would apply.

Hughes: The restrictions are unrelated to the fact that DNAX is a commercial enterprise?

Kornberg: Remember, that as soon as something judged to be significant is found at DNAX, a patent is applied for within days. Someone says to Ed Ching, who is currently the resident patent lawyer, "Ed, I'm going to present a paper Friday at an international

meeting." Ed could say, "No, you're not. We've got to make a patent application first." Instead Ed will say, "Okay, I'm going to stay up late the next two or three nights in order to file a patent application." He's also a molecular biologist; he's done a lot of postdoc work, and he's very helpful. He'll say, "Well, here are some questions," that are reasonable to have answered for a patent application, and they can be very important research questions.

Hughes: Do you believe that universities should put limitations on a professor's relationship with an industry in which he has a vested interest?

Kornberg: We'd have to particularize. I can see instances in which, emphatically, my answer would be yes. If the professor is engaged in a commercial venture that is similar to or overlaps his academic activities, it can pose very serious problems either at the level of the science or the equity involved. And if we enlarge that question to ask, should the university be involved in ventures that overlap its interests?, my answer is, even more so. I think it is very serious to contaminate academic activity with business interests.

The most serious of all is the illusion that a university with budgetary stringencies can solve a significant amount of its problems by engaging in such commercial ventures. There is an occasional instance, such as the Cohen-Boyer patent, but it is unique. That patent brought Stanford eighty million dollars over a period of fifteen years. Okay, so it brings three million dollars a year. What is Stanford's budget from the NIH? Two hundred and fifty million dollars a year. Is that going to solve research problems here, especially since that money is strictly allocated to one particular group within Stanford? University administrators and their boards of trustees simply don't understand that. They are obtuse on that issue. There is a certain amount of greed, amount of prestige in beating out some other institution for wealth.

The consequences of it are very serious because it does inevitably compromise an unadulterated openness and search for new knowledge. This is not theoretical; the situation exists at virtually all universities. Those that don't have such programs are envious and goaded by their boards of trustees to get into the act.

Anti-Semitism

Hughes: Please comment on your experience of anti-Semitism.

Kornberg: I was one of a quota of two Jewish students admitted to the University of Rochester Medical School in 1937. My disappointment with the venerated don of medical education and science at the university, George Whipple, is well known to people at Rochester. Jay Stein, who is now the vice chancellor of the medical school, was arranging for my visit in June [1997]: "Your lecture will be attended by many people and the only auditorium we have that is large enough bears the name of someone you're not happy with. Is it all right with you?" I said, "Look, I know it's the Whipple Auditorium. Of course it's all right with me."

Wherever I go and recall the history of those times, anti-Semitism was rampant everywhere. It was true at UCLA; it was true at Stanford; it was true throughout the Midwest--Illinois, Wisconsin. I think Joshua Lederberg was the first Jewish assistant professor appointed at Wisconsin. But by that time he was a sensational star. A letter describing Lederberg said, he is so brilliant, and he really doesn't have all the bad features of people of his race.

Johns Hopkins was among the worst. Barry Wood knew Johns Hopkins well. He had been a sensational All-American athlete at Harvard. He became professor of Medicine at Washington University at a very young age. He eventually wanted the job in Microbiology given to me. Having done clinical medicine, he wanted to do something important in basic science. A search committee to find a chairman for Microbiology knew of Barry's interest in the job but wanted someone more qualified in science, and offered me the job. Barry was very gracious. He went on to be chairman of Microbiology and vice chancellor of the medical school at Hopkins. At that time, Hopkins had not offered an appointment to an outstanding young ophthalmologist, Bernie Becker, and Washington University did. Barry said to me, "You know, Hopkins has done it again. They've lost a most promising young star because of their anti-Semitic stance."

When Barry appointed people to his department at Hopkins, he chose Dan Nathans, who was Jewish. On the other hand, Biochemistry, chaired by Al[bert] Lehninger who wrote the most important textbook in biochemistry--and a good friend of mine--didn't have a Jewish person in his department for twenty years, during a time when biochemistry was densely populated by Jews, either from Europe or home grown. Why not? He's dead now; I

never approached him about it. I'm guessing that he aspired to be part of a social set and a country club that didn't admit Jews and extended that discrimination in his department.

Prejudice against Jews has existed for two thousand years, not unlike the prejudice that exists against blacks. Despite all the assimilation and proactive efforts to remove it, these prejudices are going to be around for a long time. It will crop up, and it does, when you see reports about this or that desecration of a cemetery, a synagogue, a black church.

I think it is important to be reminded that, like some virus, anti-Semitism is endemic. For that reason, I want my students and my children, to whom anti-Semitism is completely foreign, to know that as recently as in my lifetime, it could be severe and ugly. I could flesh out more experiences like mine. Jewish colleagues who have written autobiographies and have had the opportunity to speak out have not done so. I don't know why. It isn't that easy.

Hughes: According to your book, members of your graduating class at City College had trouble getting jobs after they graduated.¹

Kornberg: Yes, I was at the 150th anniversary of City College a week ago, and they are very proud of their most important alumnus-- Colin Powell. He was feted beyond description.

But the previous evening, the chemistry department celebrated its 150th anniversary. Jerome Karle and Herbert Hauptman were there. There were two others in my class who got Nobel Prizes: Leon Lederman, a chemistry-physics major, and Julius Axelrod. Two of these Nobel Laureates couldn't get into medical school. One couldn't get a job. And that experience was repeated over and over again.

Columbia University had an endowed scholarship for a medical student from City College, which hadn't been awarded for nine or ten years because Columbia, just a few blocks away from City college, didn't accept any of its graduates. We got rejections, en masse, from virtually every medical school. It was an ugly scene.

African Americans who make it out of their ghetto into the NBA (National Basketball Association) earn money and fame, but they represent a tiny fraction of those who are qualified and aspire to it. The same was true of medical school admission

¹ Enzymes, p. 310.

from City College in the mid-thirties. Very few made it. Others went on to do something different, and a few became accomplished in other ways. But how about all those who dropped out, whose lives or talents were blunted? It was tragic.

Greatest Contribution

Hughes: What do you consider to be your greatest contribution?

Kornberg: The oral history that I'm giving Sally Hughes. [laughter]

Hughes: I'm asking a serious question.

Kornberg: My contribution to science?

Hughes: Whatever you like.

Kornberg: I've answered it in my autobiography; I've said that if I rate my contributions as a teacher, administrator, author, and scientist, scientist comes first. The other things depend on it. Now as a scientist, what do I rate as my major contributions? The facts that I've supplied, the attitudes that my work sustained over many years have generated, the school of scientists that I've created and sustained? Those are very difficult things to answer. Some people would say that the Department of Biochemistry, which is unique, could be regarded as my greatest achievement.

Hughes: How do you feel?

Kornberg: I wouldn't say that. But I don't think it's a minor achievement, and I'm proud of it. And it stems from several things that I've done which is to maintain scientific standards, to be a decent person, to be generous (out of long-term self-interest), and to have some luck in picking people and avoiding or disposing of some others. As for self-interest, this department provided me with an atmosphere in which I spend most of my time, that is congenial and inspiring. So much so, that I don't want to retire and give it up.

Hughes: I can see that.

Kornberg: Well, Sally, we will meet again.

Hughes: We will meet again. Thank you, Arthur.

people, taught old-fashioned bacteriology ^{in which} where you carry out certain procedures ^{to} and determine the ^{bacterium} organism by staining or other means. ^{Some} [^] ~~and~~ ^{The} ^{was} [^] focus on the pathogenesis of the disease for which the particular bacillus or coccus ~~or something else~~ is responsible. When I listened to a few of the lectures, it was apparent how inappropriate it was to teach microbiology ^{which} ~~the department had been renamed at my request~~ in these very narrow practical ways. I was accustomed to ^{The all} ~~that~~ orientation [^] from ^{having been} ~~being~~ a medical student, but that was fifteen years earlier and I was [^] ~~now~~ imbued with biochemistry and genetics.

Hughes: And you had been exposed to van Niel's approach--

Kornberg: --as a general microbiologist. He was ^{neither} ~~not~~ a biochemist [^] or a geneticist but a good general microbiologist. ~~So~~ [^] my recruiting [^] (of new faculty) was in the direction of introducing the modern aspects of biochemistry and genetics into microbiology.

Hughes: Had you been recruited with that understanding?

Kornberg: ^{but} No, there was no deception. My patrons there and particularly [^] Carl Cori, [^] ~~who was~~ the most distinguished member of the faculty, knew what I was [a biochemist] and what I wanted to ^{in research,} do. [^] As far as teaching was concerned, well, it would take care of itself.

After ^{a year or two} ~~[my] first or second or third year~~ [^] of teaching, [^] ~~at~~

Washington University^g, the students, who ^{had taken} took biochemistry in their first year, dubbed our course Biochemistry II. ^{Our course STET} It was ^{not} anything but well received. ^A The fifth column, ^{constituted} of several people ~~who were~~ left over [✓] from the old department, [✓] would tell the students that they weren't learning [✓] [medical] bacteriology ^{and} [✓] they were being deprived of exposure to [✓] [information about] syphilis and other [✓] [diseases] [✓] that would be crucial to ^{becoming} their being legitimate M.D.'s. [chuckles]

I might say as a postscript that in subsequent years the students we had those years, ^{either} ~~now~~ practicing M.D.'s or in academic medicine, would refer to that course as the most memorable and enlightening course that they had had. That was ^{not only} [due] to the curriculum, ^{but} ^{and} also to ^{the} the spirit of the young people who were teaching ^{the} [the course], ^{they were} teaching subjects that they ^{hadn't} ~~didn't~~ know anything about, ^{but} ~~that they were~~ learning ^{at} ~~the~~ same time ~~[as the students].~~ ^{with novel} ~~new~~ insights.

Hughes: Did you have a model for the curriculum?

Kornberg: That's the point; there was no model; ^{we had} ~~there was~~ no textbook. The famous textbook by [Bernard] Davis ^{and co authors} ~~et al.~~, which included ^{only} some eminent people, came out years later. ^{We had} ~~So that was~~ another point: ^{there was} ~~there was~~ no book ^{that} ~~that~~ the students could consult to capture this new attitude about the importance of biochemistry and genetics ^{for} ~~to~~ learning about microbes, whether they ^{were} ~~are~~ good

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Education: 1937 B.S., City College of New York
 1941 M.D., University of Rochester

Professional Background:

1941-1942 Intern, Strong Memorial Hospital, University of Rochester
 1942-1953 Commissioned Officer, U. S. Public Health Service
 1947-1953 Chief of Enzyme and Metabolism and Metabolism Section of
 National Institute of Arthritis and Metabolic Diseases, National
 Institutes of Health, Bethesda, MD
 1953-1959 Professor and Head, Department of Microbiology, Washington
 University School of Medicine, St. Louis, MO
 1959-1969 Chairman, Department of Biochemistry, Stanford University
 School of Medicine, Stanford, CA
 1959-1988 Professor, Department of Biochemistry, Stanford University
 School of Medicine, Stanford, CA
 1988- Professor *Emeritus* (Active), Department of Biochemistry,
 Stanford University School of Medicine, Stanford, CA

Honors:

1951 Paul-Lewis Award in Enzyme Chemistry
 1959 Nobel Prize in Medicine (with Dr. S. Ochoa)
 1965 President, American Society of Biological Chemists
 1970 American Philosophical Society
 1970 Foreign Member, Royal Society
 1979 National Medal of Science
 1960- Honorary degrees: City College of New York, Washington
 University, University of Rochester, Yeshiva University,
 University of Pennsylvania, University of Notre Dame,
 Princeton University, Colby College, University of
 Barcelona, University of Paris, Medical College of Wisconsin,
 University of Miami
 1995 Cosmos Club Award
 1995 Gairdner Foundation Award

Organizations:

National Academy of Sciences
American Philosophical Society
Board of Governors, Weizmann Institute
Foreign Member, The Royal Society
Founder, Member of the Policy Board, Executive Committee and the
Scientific Advisory Board - DNAX (Div. of Schering-Plough Corp.)
Scientific Advisory Board - Regeneron Pharmaceuticals
Board of Directors and Scientific Advisory Board - XOMA Corp.
SAB - GalaGen.

Books:

Enzymatic Synthesis, John Wiley & Sons, 1961
DNA Synthesis, W. H. Freeman and Co.,
San Francisco, 1974
DNA Replication, W. H. Freeman and Co.,
San Francisco, 1980
DNA Replication (2nd Edition) with Tania A. Baker.
W. H. Freeman and Co., New York, 1992
For the Love of Enzymes, Harvard University
Press, 1989
The Golden Helix: Inside Biotech Ventures
University Science Books, 1995

Arthur Kornberg Biographical Sketch

Arthur Kornberg was born in Brooklyn, New York in 1918 and educated in its public schools. He received his undergraduate degree in science from the City College of New York in 1937 and the M.D. degree from the University of Rochester in 1941. After a year's internship in internal medicine, he served as a commissioned officer in the U. S. Public Health Service. He was first assigned to the Navy as a ship's doctor, and then as a research scientist at the National Institutes of Health (NIH) in Bethesda, Maryland, from 1942 to 1953. He obtained training in enzymology with Professor Severo Ochoa at New York University School of Medicine in 1946 and with Professor Carl Cori at Washington University School of Medicine in 1947. Upon returning to Bethesda, he organized and directed the Enzyme Section. He resigned in 1953 with the rank of Medical Director, to assume the chairmanship of the Department of Microbiology of Washington University School of Medicine in St. Louis, Missouri. In 1959, he organized the Department of Biochemistry of the Stanford University School of Medicine, serving as its chairman until 1969 and thereafter as professor. He accepted the title of Professor *Emeritus* in 1988 and has been on active status to the present.

From his early studies of the mechanisms of the enzymatic synthesis of coenzymes (NAD, NADP, FAD) and inorganic pyrophosphate, he extended his interest to the biosynthesis of the nucleic acids, particularly DNA. After elucidating key steps in the pathways of pyrimidine and purine nucleotide synthesis, including the discovery of PRPP as an intermediate, he found the enzyme that assembles the building blocks into DNA, named DNA polymerase. This ubiquitous class of enzymes make genetically precise DNA and are essential in the replication, repair and rearrangements of DNA. Many other enzymes of DNA metabolism were discovered responsible for the start as well as the elongation of DNA chains. In recent years, enzyme systems were discovered which initiate and terminate the replication of a chromosome, crucial events in the life cycle of a cell.

Since 1991, he switched his research focus from DNA replication to inorganic polyphosphate, a polymer of phosphates that likely participated in prebiotic evolution and is now found in every bacterial, plant and animal cell. Neglected and long regarded a molecular fossil, inorganic polyphosphate

has a variety of significant and putative functions that deserve biochemical study.

Although the pursuit of research has been his primary concern, other interests include the formal teaching of graduate, medical and postdoctoral students, and the authorship of major monographs: DNA Synthesis in 1974, DNA Replication in 1980, Supplement to DNA Replication in 1982, and DNA Replication, Second Edition, in 1992. A scientific autobiography, For the Love of Enzymes: The Odyssey of a Biochemist, Harvard University Press, appeared in 1989. The Golden Helix: Inside Biotech Ventures, University Science Books, was released in July of 1995, and provides an insider's view of biotechnology.

In his academic career, he has served as departmental chairman, on the committees of the Medical School and university, as president of the American Society of Biological Chemistry (1965), and on the advisory boards and councils of numerous university, governmental and industrial research institutes. He is a founder of the DNAX Research Institute of Molecular and Cellular Biology (a Division of Schering-Plough, Inc.), and a member of its Policy and Scientific Advisory Boards. He serves on the Scientific Advisory Boards of Regeneron Pharmaceuticals, Inc., GalaGen, and the XOMA Corp., and is also a member of the Board of Directors of XOMA Corp.

Among his honors are memberships in the National Academy of Sciences, the Royal Society, American Philosophical Society, a number of honorary degrees, the Nobel Prize in Physiology or Medicine (1959), the National Medal of Science (1979), the Cosmos Club Award (1995) and other medals and awards.

He was married in 1943 to Sylvy Ruth Levy, who died in 1986. He has three sons and eight grandchildren. Roger is Professor of Cell Biology at Stanford; Thomas is Professor of Biochemistry and Biophysics at the University of California in San Francisco; Kenneth is an architect and founder of Kornberg, Associates in Menlo Park and Delmar, California, specializing in laboratory design. In 1988 he married Charlene Levering, who died in September of 1995. Dr. Kornberg resides in Portola Valley, California. He enjoys tennis, travels, music and time with his family.

Publications of Arthur Kornberg

1. Kornberg, A. , Latent Liver Disease in Persons Recovered from Catarrhal Jaundice and in Otherwise Normal Medical Students as Revealed by the Bilirubin Excretion Test, *J. Clin. Inves.* , XXI, 299 (1942).
2. Kornberg, A. , Daft, F. S. , Sebrell, W. H. , Production and Treatment of Granulocytopenia and Anemia in Rats Fed Sulfonamides in Purified Diets, *Science*, 98, 20 (1943).
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6. Kornberg, A. , Tabor, H. , and Sebrell, W. H. , The Effect of L. Casei Factor ("Folic Acid") on Blood Regeneration Following Hemorrhage in Rats, *Am. J. of Physiology*, 142, 604 (1944).
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Budgetary restraints increase the pressure both in academia and industry to do strategic, targeted, goal-oriented research. But we need to be reminded that throughout the history of medical science the major advances in diagnosis, prevention and treatment of disease were based on the curiosity of biologists, chemists and physicists unrelated to the ultimate applications of this basic knowledge to the development of drugs and devices. The extent of support for costly basic research, seemingly irrelevant and arcane, in budgetary competition with imperative and urgent social programs, is a current issue of great concern.

Basic Research vs. Clinical Crusades

Contrary to common logic, the most cost-effective way to cope with cancer, degenerative diseases and viral scourges, like AIDS, is to fill the huge gaps in our knowledge of the basic biology and chemistry of cells, from the microbial to the human. One need only to recall the dramatic advances derived from creative, untargetted research compared with the lack of success to date of cancer crusades and the war to cure AIDS.

X-rays were discovered by a physicist observing discharges in vacuum tubes, penicillin came from enzyme studies of bacterial lysis, and the polio vaccine from learning how to grow cells in culture. Cisplatin, a widely used drug in cancer chemotherapy, came about from studying whether electric fields affect the growth of bacteria and then observing an inhibition traced to the unexpected electrolysis of the platinum electrodes. Genetic engineering and recombinant DNA depended on reagents developed in exploring the biochemistry of DNA.

The breakthroughs in biotechnology were made in academic laboratories built and supported almost entirely by funds from the National Institutes of Health. For thirty years, my research on the biosynthesis of the building blocks of nucleic acids, their assembly in DNA replication and the training of over a hundred young scientists, was funded with many millions of dollars without any promise or expectation of marketable products or procedures. No industrial organization had, or would ever have, the resources or disposition to invest in such long-range, apparently impractical programs. We carried out these studies to satisfy our curiosity. Yet to my pleasant surprise such studies of the replication, repair and rearrangements of DNA have had many unanticipated practical benefits. The pathways of assembling DNA from its building blocks have been the basis for the design of most drugs used in the chemotherapy of cancer, AIDS, herpes and the treatment of autoimmune diseases. These studies are crucial to understanding the repair of DNA, so important in the aging process, for understanding mutations, and the origin of some cancers.

In sharp contrast to the success of investments in basic research, are the twenty-five years of disappointing research too narrowly focused on cancer at the cost of over a billion dollars a year, the futility of lung machines to palliate polio, and the ten-year discouragement in curing AIDS for lack of

essential facts about the human immune system. In fact, the major advances in understanding cancer and AIDS emanate from the basic research that discovered the oncogenes of cancer and promptly identified HIV as the cause of AIDS. Without innovation, our weaponry to combat disease will remain inadequate and suffer obsolescence.

Long-Term Support of Basic Research

How can we convince people to support basic research? Perhaps the analogy of rearing a child would help. We accept the uselessness of an infant, the cost of its education and support for more than twenty years in the hope of producing a useful citizen. In the same vein, we need to explain that basic research also follows a tortuous, uncertain route and needs to be supported for a long time to produce the practical advances for medicine and industry.

Sustained education and persuasion for the support of basic research cannot be left to scientists and their societies; their amateurish approach and incapacity as a political force has been demonstrated for decades. Nor can we rely on the spirit and vision of the rare evangelist—a Mary Lasker—to persuade beleaguered congressmen to favor an unorganized and powerless constituency. Clearly, what is needed is a permanent, well-funded organization to secure the nonpartisan, long-term commitment of the Congress for the preservation of the nation's health and economic well-being through vigorous science and technology.

The budget for the National Science Foundation, vital for the support of research and training in basic physics, chemistry and math, is at present in limbo. The recent, much-heralded rescue of the NIH budget with a puny 5.7% increase is due to the patronage in Congress of John Porter and Newt Gingrich, who had to inform many of their colleagues what the NIH acronym meant and how this most brilliant social invention of the 20th century has revolutionized medical science worldwide. The facts are that this NIH budget still fails terribly to exploit the large resource of highly trained and motivated scientists poised to make the rapid advances that the new technologies have made possible. The current NIH budget in basic research is a feeble investment, less than 1 percent of the national expenditures on health care. Were this sum significantly increased, we could reap a vast return in the reduced cost and better care by advances of medical technology.

How to Support Basic Research

It is an utter illusion to expect industry and philanthropy to support the gap in federal support of basic research. In the past and for the foreseeable future, well over 90 percent of support must come from federal sources. Universities and research institutes, now engaged in desperate competition with each other for the very limited resources supplied by heart, cancer and other disease-oriented societies and by generous individuals and foundations, should instead unite their efforts and money to fund an organization that would finance and reward the campaigns of congressmen to dispose them to support basic research. Money matters. If the National Rifle Association can be so successful politically in its mission, why can't health science do at least as well with a far better message? If industrialists and activists were recently

able to agree on environmental safeguards, why can't pharmaceutical manufacturers, and insurance companies unite with physician groups, scientists, universities and heart and cancer societies to insure a long-range policy to advance basic research in medical science?

Scientists are repeatedly implored to make the case for basic science with the electorate and Congress. But scientists are self-selected for their interest in molecules, cells and small organisms rather than for social and political skills. Unlike physicians, lawyers, businessmen, postal carriers and most others, they are a fragmented constituency with little inclination for organized actions, except to hold scientific meetings and publish journals. When scientists do bestir themselves, their efforts are spasmodic and inadequate. Those few scientists with some talent in public affairs, find that even brief forays in the political world diminish their stature and credibility as scientists. Yet scientists in every locality can and will contribute in an effective way, if called upon, to meet with citizen groups and congressional staffs, give accounts of their efforts, hopes and successes that will fortify the message that "basic research is the life line of medicine."

There is nothing base or narrow in organizing and operating a national organization to promote health science. With proper organization and leadership, grass roots support can be developed in every Congressional district. Individuals and institutions should be persuaded that their contributions can be leveraged ten-fold or more by joining a common effort rather than engage in pitched competition. As an example, one million dollars invested by a Stanford donor to promote a 10% increase in the NIH/NSF budgets would likely return well in excess of \$10 million for basic research at Stanford.

Conclusions

Support for basic research must be utterly nonpartisan and long-term to persuade people to enter careers in science, to pursue novel ideas and to feel assured that changes in political administration will not affect the progress of science in America. To obtain this long-term, nonpartisan support of basic research, so essential for the health and economy of our nation, we need a permanent, well-financed, professional organization rooted in every Congressional district. Scientists would contribute eagerly at this level.

With the right leadership, this new organization can build on and leverage the existing skills and good will of the numerous groups already dedicated to improving the technological base for the prevention and treatment of disease and for providing the next generation of creative scientists.

Arthur Kornberg

Basic Biomedical Research

We invite you to join us in an organization to promote the expansion of federal funds in the long-term support of basic biomedical research. The novel features of this organization are:

- Long-term (5-10 years) support rather than spasmodic (annual) commitments.
- Dues-paying members who would provide \$2-3 million annually, supplemented by other contributors.
- A Washington office employing about 20 people who would provide full-time, professional services in the education of legislators and mobilization of constituencies in every congressional district.
- Speak with one (unfragmented) voice for all of biomedical research.
- Complement the ongoing efforts of Research America, professional societies, disease-focus groups, universities, etc.
- Invite scientists (and their students) in every community to appear before benevolent groups to inform them of their

ongoing research and relevance to global questions in
biomedical science.

We are responding to the repeated criticisms that scientists are not active in making the case for basic biomedical research in local and national politics. The proposed organization will meet that issue in two ways: one, to employ skilled professionals to make the case for them, and two, to become engaged directly in scientific contexts with constituencies at the community level.

The initial financing of this organization is underwritten by those identified on this letterhead. Will you join us with an annual pledge of \$100 or more? Creation of this organization will depend in your pledge.

→ Sally Hughes

August 24, 1997
ASBMB -San Francisco

Centenary of the Birth of Modern Biochemistry

I feel moved to have been asked to present the Keynote Lecture to this Congress. I am deeply grateful to Bob Hill, Chairman of the Organizing Committee and to the members of the Committee for this honor. It is a major prize and I cherish it.

To all of you here, colleagues from around the world, I give you my most hearty greetings. Having been close by at Stanford for nearly 40 years, I feel qualified to be your host in the Bay Area. I grew up in Brooklyn, N. Y., went to medical school in Rochester, N. Y., spent 10 years at the NIH in Bethesda, and then six at Washington University in St. Louis. St. Louis, as you may know, regards itself as "The Gateway to the West." But when the chance came for me to move west to California, I took the gateway literally. While I was living in the East and Midwest, I was irritated by boasts by Californians about the wonderful geography, the fabulous climate, and the great food in San Francisco. Now, I've learned that the boasts were not exaggerated.

There's a story about two women from Boston who were visiting here some years ago and having dinner at Fisherman's Wharf. One said to the other: "Mabel, I had no idea the fish could be so good, 3000 miles from the coast."

To those of you who are visitors to the Bay Area, I suggest that after San Francisco, you drive over the Golden Gate Bridge to see the giant redwoods in Muir Woods. And about an hour's drive north from here you can get to the Point Reyes Seashore Park, best reached by Lucas Valley Road. There you'll find many trails with spectacular seascapes and lovely meadows; on the Tomales Point trail, there are herds of wild elk. Or you might drive south--about 2 hours away-- to Carmel and nearby Point Lobos Park. The park encapsulates the most dramatic meetings of sea and shore on any coast.

People are anniversarial! Every year there are anniversaries to celebrate, most notably, centenaries. Ten years ago we celebrated the centenaries of the founding of the NIH and the Pasteur Institute. 1997 is no exception. In 1997, we can celebrate several centenaries: the centenary of the discovery of the electron by J. J. Thomson. That discovery, along with other

momentous advances around that time, brought in the golden half-century of modern physics. Also in 1897, C. W. Post introduced grape nuts, incidentally, a cereal with neither grapes nor nuts, but it revolutionized breakfast around the world. We could also celebrate the centenary of Jell-O. Most seriously and significantly, it was in 1897 that Eduard Büchner accidentally observed that a yeast juice could convert sucrose to ethanol. That discovery at once disposed of the firm Pasteurian belief that alcoholic fermentation is a vital operation of an intact cell. It was the discovery of cell-free fermentation that set the stage for modern biochemistry.

The forty years of enzyme fractionation that followed finally resolved this so-called "zymase" activity into the now-familiar, dozen discrete reactions. The reconstitution of alcoholic fermentation, a phenomenon that had baffled scientists for centuries, was defined in molecular terms. This triumph of enzymology and its many applications became a major source of the extraordinary advances of biomedical science in this second half of our century.

The development of enzymology after Büchner was exceedingly slow by modern standards. When we reflect on progress in biomedical science in this century, the early decades were still dominated by the microbe hunters who were then replaced in the spotlight by the vitamin hunters. It wasn't until the 4th and 5th decades that the enzyme hunters occupied center stage, only to be replaced in recent decades by, you know who: the gene hunters. Who will succeed them in the coming years is of course a matter of speculation. Perhaps the neurobiologists and neurochemists unraveling the functions of the brain. What will they be called? The head hunters?

During the 20th century with its succession of hunters and golden ages in medical science, the current age of genetic engineering and related biotechnologies represent the most revolutionary advance in the history of biological and medical science. The term revolutionary is generally overused, but not here. The effects of this advance on medicine, agriculture, industry and basic science have not been exaggerated.

Also revolutionary, but generally unnoticed, is a development which lacks a name or obvious applications. Yet, I believe it will lead to even more remarkable discoveries and unanticipated applications. I refer to the coalescence of all the biological and medical sciences, previously discrete, into

a single, unified discipline. This discipline has emerged because it is expressed in a single universal language, the language of chemistry.

Much of life can already be understood in rational terms if expressed in the language of chemistry. It is an international language, a language without dialects, a language for all of time, and a language that explains where we came from, what we are, and where the physical world will allow us to go. Chemical language has great esthetic beauty and links the physical sciences to the biological sciences.

Attention to enzymology and biochemistry has been diminished by the advent of molecular biology and the glamour of genes and genomics. For these reasons, it is worth noting what the classic biochemical disciplines have provided conceptually and practically to science and particularly to the very emergence of biotechnology. Enzymology solved problems of cellular chemistry, it made available the reagents for recombinant DNA and genetic engineering, and it provided essential links between chemistry and physiology.

That enzymology can solve chemical and biological problems is based on the fact that virtually all biologic operations are catalyzed, directed and regulated by enzymes. Spontaneous reactions in cells are rare: hydration of CO₂ depends on carbonic anhydrase; melting of DNA is catalyzed by a variety of helicases; and hybridization of DNA chains is facilitated by DNA-binding proteins. Although organic chemists were reluctant to recognize enzymes, let alone use them, others, Gobind Khorana for example, exploited the awesome specificity and catalytic efficiency of enzymes to achieve the total synthesis of the gene for alanine t-RNA. In the epochal Watson and Crick paper on the double-helical structure of DNA in 1953, the only flaw I can find is their suggestion that were nucleotides, aligned by base pairing to a DNA template, they would polymerize spontaneously.

The first task of the enzymologist in reducing a biologic event to molecular detail is to observe the event in a cell-free system. Then the effort can be made to resolve and reconstitute the event. Beyond the classic examples of alcoholic fermentation and the synthesis and utilization of glycogen, more recent ones include the elucidation of gene expression and the replication, repair and recombination of DNA. In a cell-free system, the biologic event can be performed even better by the biochemist than by the intact cell. After all, the cell is constrained in a consensus medium to sustain

thousands of diverse reactions. By saturating enzymes with substrates, trapping products and providing the optimal pH, metal ions, ionic strength and cofactors, the biochemist gains a more precise understanding of enzymes, mechanisms and pathways and their ultimate relation to physiologic operations.

Compared to the horse and buggy days of the early enzyme hunters, modern methods of fractionation and micro analysis have made the isolation of enzymes a jet-age operation. But the most remarkable feature of current enzymology is reverse genetics and the availability of genome sequences. A minute quantity of a polypeptide enables us to identify and clone its gene, knock out the gene and overexpress it, and, with those maneuvers, gain major insights into the physiological functions of the enzyme. Often ignored is the capacity to produce large quantities of an enzyme for mechanistic studies and for use as a reagent to analyze its substrate and prepare its product.

In my recent work I have been exploring the functions of inorganic polyphosphate, a mysterious and ubiquitous polymer of hundreds of phosphate residues. I have approached the problem by isolating enzymes that make the polymer and other enzymes that degrade it. The purified enzymes have been crucial. They have provided for the first time, exceedingly rapid, sensitive and definitive assays for polyphosphate, the means to synthesize radioactive chains of defined length, and have opened the door to structural studies, reverse genetics and physiology.

Beyond my deep faith in enzymes, I adhere to a second faith, the universality of biochemistry. During the course of resolving the alcoholic fermentation in yeast juice, glycolysis by a muscle extract was also resolved into its molecular components. Astonishingly, the muscle pathway was virtually identical to that of yeast. And the same proved to be true since then of the many bioenergetic and biosynthetic pathways. Clearly, mechanisms and molecules have been highly conserved for a billion or more years in bacteria, fungi, plants and animals. To my mind, the universality of biochemistry represents one of the great revelations of our century.

My faith in the universality led me in forty years of work on DNA replication to focus on *E. coli* where the replication of its genome, phages and plasmids is completed in minutes rather than hours. In recent studies of eukaryotic replication, there have been fascinating revelations, but the mechanisms and molecules have proved to be variations on themes familiar

from prokaryotic work. In a similar vein, the exciting advances in genes and genomes have been made with the confidence that the genetic code and the enzymology of gene expression are universal and interchangeable.

In biochemical science, we now possess phenomenal capacities to acquire and integrate unprecedented quantities of sophisticated data. Yet, in this time of informational plenty, we are beset by many serious problems, some of which threaten the foundations of our huge scientific enterprise. For the sake of brevity, I have selected just three among the problems which warrant our concern.

The three problems I want to consider are the antiscience attitudes in society, the consequent lack of support for basic science, and several conflicts and schisms within our science. The first problem is the rising tide of public fear, distrust and rejection of science, both chemical and biological.

Chemistry has had a poor image for some time. "Better things for better living. . .through chemistry" had been the DuPont slogan for many years. The slogan has now been abbreviated to: "Better things for better living." The words "through chemistry" were dropped. Last year the largest banks in New York merged: Chase Manhattan and the even larger Chemical Bank. Not surprisingly, the new giant bank is simply the Chase Manhattan. There is no "chemical" in its name. In fact, the only times we hear something good said of chemistry these days are references, as in newspaper articles, to the good chemistry of a winning football team, or the improved chemistry among managers of a profitable corporation.

The image of biologists has not been doing well either. Hollywood has chosen them as their villains in recent years. Lacking communists as culprits, and squeamish about racial bashing, some hit movies have demonized doctors and scientists - "Lorenzo's Oil," "The Fugitive," and "Jurassic Park".

And then there are those disillusioned with the failure of science to cure the ills of society. Vaclav Havel is a major culprit. This celebrated Czech author and statesman and his followers blame modern science for degrading the natural world and bringing us to an abyss.

The mass suicide a few months ago of the Heaven's Gate commune is a tragic example of thinking in our advanced civilization. In the New Yorker magazine, Timothy Ferris described how early this year the commune bought an expensive telescope to look for a gigantic alien spacecraft accompanying the Hale-Bopp comet. When they failed to find it, they blamed it on the

inadequacy of the telescope and returned it to the dealer. To quote Ferris: "Though science is stronger today than when Galileo knelt before the Inquisition, it remains a minority habit of mind, and its future is very much in doubt. Blind belief rules the millennial universe, dark and rangy as space itself."

As a result of an uninformed or misinformed public, we have a second problem, the lack of adequate financial support for science, a poverty worsened by severe pressures to engage in targeted research such as the treatment of breast cancer, and AIDS or the development of technologies to improve the economy.

Strategic plans for medical research are repeatedly proposed and imposed. The plans are fundamentally flawed because discoveries are commonly serendipitous. The best plan for medical advances over many decades has been no plan. For lack of essential knowledge, timetables for assaults on particular disease targets have had little meaning. Nor could we have anticipated the confrontations with novel diseases.

It may seem unreasonable and impractical, call it counterintuitive, even to scientists to solve an urgent problem, such as a disease, by pursuing apparently unrelated questions in basic biology or chemistry. Yet, the pursuit of understanding the basic facts of nature has proven throughout the history of medical science to be the most practical, the most cost-effective route to successful drugs and devices.

Investigations that seemed totally irrelevant to any practical objective have yielded most of the major discoveries of medicine - X-rays, penicillin, polio vaccine, Cis-platin, recombinant DNA and genetic engineering. All these discoveries have come from the pursuit of questions in physics, chemistry and biology, unrelated at the outset to a specific medical or practical problem.

With regard to industrial inventions: "Necessity is not the mother of invention." Rather, the reverse has proven to be true: Invention is the mother of our necessities. Inventions only later become necessities!

Time and again, inventors created things that had to wait many years to be recognized for their practical value. Nobody really needed the airplane, the FM radio, television, lasers, the transistor or the quantum mechanics, that led to the transistor. Take xerography. It took Chester Carlson, the inventor of the Xerox process, six years to interest the Haloid Corporation in his

invention and twenty years before the first commercial copier was produced. FAX machines were invented 30 years ago, but it took a deteriorated postal service among other factors to make them the necessities they are today.

Quite clearly, even industrial inventions emerge from a creative process. As such they are haphazard rather than goal-oriented. The lessons to be learned from this history should be crystal clear. It is crucial for a society, a culture, a company, a university, to understand the nature of the creative process and to provide for its support. No matter how counter-intuitive it may seem, basic research is the lifeline of practical advances in medicine; pioneering inventions are the source of industrial strength. The future is invented, not predicted.

The overriding issue in biomedical science, as I see it, is how to give our abundant scientific talent the resources to exploit the extraordinary new technologies to advance knowledge. Currently, a pervasive mood among productive biomedical scientists makes them fear for continued grant support, persuades them to choose safe and practical projects over the untried and adventurous, and tempts their interest in commercial ventures. This is clearly a state that discourages young people from entering science and drives others to abandon science for business, law and other pursuits.

Scientists are beseeched to make the case for support of biomedical research with their fellow citizens, to be fund and friend-raisers in the community, and to persuade their congressmen to increase the federal budgets for research. Then they are berated for doing none of these things. Their friends in the community and in the Congress fail to realize that scientists, as a group, are self-selected for their interest in molecules and cells and their disinterest in people and politics. Unlike virtually every other professional group—doctors, lawyers, businessmen, pilots—scientists fail individually and collectively to lobby for their cause.

The most prestigious of our scientific societies, the National Academy of Sciences, through its National Research Council, makes awesome contributions to the whole world of factual information from highway construction to child care. Yet, as a matter of policy, the Academy refrains from efforts to maintain, let alone increase federal support for basic research. With regard to the lobbying efforts of the major scientific societies and other organizations, they have, despite occasional heroic interventions, been amateurish and grossly inadequate. They are heard as pleadings from

splintered, divisive, incoherent and unfocused constituencies. They fail to inform our administrators, legislators and their fellow citizens of the value of basic biomedical research.

For the long-term support of research and training, we need a national organization of dues-paying biomedical scientists to sustain a large, full-time professional group in Washington to convey the message: "If you think research expensive, try disease." The message must be delivered daily to legislators and, with the help of scientists, in every Congressional district. I believe that our fellow scientists will respond to requests to describe their research to lay groups in the community and convince them that throughout the history of medical science, the major advances in diagnosis, prevention of and treatment of disease, have come from the pursuit of knowledge by biologists, chemists and physicists, pursuits unrelated to the ultimate application of this basic knowledge to the development of vaccines, drugs and devices.

Well over 90% of the past and current support of basic biomedical research has come from the federal government and always will. Support by industry and philanthropy can be helpful and catalytic, but will never be sustained and substantial. Training and research in biomedical science is an essential investment by the nation of a magnitude that only our federal government can make.

The final problem I want to consider includes conflicts and schisms within our science: there are conflicts between the cultures of chemistry and biology, confusion in biotechnology between biology and technology, and big science versus little science. In each of these conflicts, philosophical differences are overlaid by strong economic, social and political forces.

First is the age-old rift between the cultures of chemistry and biology. It may not be as deep as the rift described by C. P. Snow between the sciences and humanities, yet it is serious enough to be counterproductive. The emergence of biochemistry might have bridged the gap between chemistry and biology but it didn't. Paradoxically, neither has the recent popularity of genetic chemistry.

As far back as 1913, F. G. Hopkins, later the doyen of British biochemistry, tried to promote what he called dynamic biochemistry, described by him "as the borderland where chemical knowledge is combined with trained instinct and feeling for biological possibilities." Although

Hopkins succeeded as the founder and chairman of a remarkably productive and eclectic Department of Biochemistry in Cambridge, that atmosphere neither survived him nor caught on elsewhere.

Chemists continue to synthesize and analyze small molecules with ever greater precision, but they neglect the biological macromolecules: the proteins, nucleic acids and polysaccharides; these seem to them too complex or too mundane. Chemists were previously reluctant to recognize or use enzymes, but some have begun to examine enzymes for their awesome specificity, chirality and catalytic efficiency. Still remote from their attention are the social faces of enzymes, the interactions with other enzymes, structural proteins, membranes and matrices that create the functional macromolecular assemblies and tissue organelles.

Biologists for their part avoid enzymology. To them, enzymes are faceless components of kits or putative gene products inferred from sequences recognized by motifs and homologies. Biologists are so enthralled by the mysteries of evolution, development, aging and diseases, that they resist reductionist chemical approaches and focus instead on the vital phenomena they create by altering the genomes of their favorite organisms.

In his day, F. G. Hopkins fought protoplasm, he fought for the reduction to molecular terms of protoplasm and all vital phenomena. But the fight against vitalism has never been won and perhaps never will be, even though the history of science is littered with wholistic pronouncements that the end had been reached and that the perimeter of ignorance would be impenetrable. I'm reminded of the Rodgers and Hammerstein lines from Oklahoma that go:

"Ev'rythin's up to date in Kansas City.

They've gone about as fur as they can go!"

F. G. Hopkins put it better in his Boyle Lecture in 1913: "The biologist has long studied living organisms and will continue to do so with ever-increasing interest. As for the biochemist, his may not be the last word in the description of life, but without his help, the last word will never be said."

To be sure, there have been celebrated hybrid chemist-biologists-- Pasteur, Hopkins, Avery and Pauling--to name a few. And there are notable hybrids in our generation, especially among a widening circle of structural biologists and chemists. But too few traditional chemists exploit the borderland, in which they can find rich harvests in the vast and awesome

chemistry evolved for over a billion years. As for biologists, application of chemical techniques of ever-increasing sensitivity and precision, would gain them a deeper and 4-dimensional understanding of biologic events.

Another conflict is found in the increasing influence of biotechnology enterprises. Genetic engineering and associated technologies have been enormously successful. They have truly revolutionized medicine and agriculture, and have created a multi-billion dollar industry with fallouts that have also profoundly advanced basic biomedical research. Yet we must be aware of problems created by this success. The very term biotechnology, adopted as a euphemism for genetic engineering, may blur the important distinction between biology, a quest for knowledge, as opposed to technology, the application of that knowledge for products and profit.

There are now over 1200 biotech companies operating in the U.S. They are not in business to do research; rather they are in research to do profitable business. These biotech ventures have filled an essential need. They take discoveries which cannot be developed in academia to a stage where, with collaboration of major pharmaceutical companies, small-scale preparations are expanded to large-scale production, where screening, clinical testing, and regulatory approvals ultimately lead to marketable products and devices. But too often, commercial pressures on biotech ventures promote secrecy, patent litigation, and an overly narrow focus on a target perceived as profitable.

Scientists and academic institutions involved in such enterprises are likely to be distracted from their central mission: the pursuit of the basic understanding of nature. I am especially concerned with another problem. There is an illusion created by the financial and research successes of a few biotech ventures that a significant fraction of basic advances can be supplied by industry. Although such achievements are laudable, they represent only a tiny fraction, perhaps five percent of the basic knowledge needed to combat diseases, advances which can come only from the massive federal support of research and training.

Lastly, I want to mention still another conflict, the schism between big and little science. Of course, we need both. There are projects that require large and expensive equipment and several disciplines to use it effectively. My concern is that with the worldwide expansion of big science, little science will vanish.

In the United States there has been a proliferation of disease centers for cancer, AIDS and a variety of other diseases. Once created, these centers grow and last forever, sustained by strong political support from organized constituencies. In each center, authority over research is vested in the Director who can shelter people and programs that would not withstand a standard peer review. The Human Genome Project recently became an institute of the NIH. It will grow long after the human and other genomes have been sequenced. What then? The current \$200 million budget of the Genome Institute could provide \$100,000 grants to each of 2,000 investigators.

In Europe, research programs, especially in the smaller countries, rely on grants from the European Union. The EU requires that investigators from three or more countries find a consensus project that can be parcelled up among them. This leaves no room for a scientist to do something utterly original and unpopular and much time is wasted on bureaucratic maneuverings. Recent news reports indicate that the U.K. is planning to consolidate grants along similar lines.

Japan should be applauded for the Human Frontier Science Program. But here again, grants are made to a group of investigators assembled from several countries who can devise a project advanced enough to be divided among their demonstrated skills and experience. Within Japan, the recent expansion of research grants is laudable but the mechanism is all too familiar: a very large sum is awarded to a "center of excellence" where the director has complete authority over what is done and who does it.

In this connection, I want to remind you that the most remarkable innovation in the history of research support anywhere in the world, we owe to the NIH. Grants are awarded to individuals, young and old, rather than to department heads, university deans or directors of institutes. Awards are made on scientific merit as judged by panels of scientists drawn from outside the government. By this means an individual, un beholden to any local administrator, becomes an entrepreneur of research and solely accountable for its success.

As I view the steady growth of collective science and big science, the greatest danger I see is a dampening of individual creativity and reversion to the old politics--the inevitable local politics that infects every group and institution.

I have focussed on several problems: the anti-science forces in society, the lack of support of basic research, and the conflicts and schisms within our science. Among these conflicts are those between chemistry and biology, between biology and technology, and between big science and little science. I could add more problems to this list. So could you. But instead, I want to recognize what deserves the most emphasis and what unites us all. It is our unconflicted and overriding devotion to the culture of science.

We must make it clear to the public that science is great, although scientists are still people. As people, they are no different from others: dentists, lawyers, artists, businessmen. Scientists are just as prey to the human failings of arrogance, greed, dishonesty and psychopathy. What does set scientists apart from others is the discipline of science, a practice that demands exact and objective descriptions of progress, evidence that can be verified or denied by others.

It is the discipline of *science* that enables all of us *ordinary* people, whether we be chemists or biologists, to go about doing the *ordinary* things, which, when assembled, reveal the *extraordinary* intricacies and awesome beauties of nature. Science not only permits us to contribute to grand enterprises, but also offers a changing and endless frontier for explorations. Despite all the problems young people face today, do I recommend a career in science to my grandchildren? Emphatically, I do!

Has the computer revolution and other advanced technologies altered the way we do bioscience research these days? Can research now be engineered and pursued by formula? Not yet. The technical and computational tools are indispensable, but the practice of science remains highly creative and its province is Nature. Sir Karl Popper, an eminent philosopher of science and society, who died a year ago in London, said that "next to music and art, science is the greatest, most beautiful and most enlightening achievement of the human spirit." I differ only in placing science first.

We probe the inexhaustible mysteries of Nature from a variety of directions and with different intensities and styles. These probings are determined by our emotions, our moods and our cultural heritage, much as these influence the artist. The major discoveries in science are more often intuitive or serendipitous than the result of logical analysis.

To be sure, the machines we use produce images and compositions of objective precision. But this should not obscure the fact that we use these machines as tools, with tastes as distinctive as those that painters use their palettes, composers their notes, and authors their words in creating their images of Nature. Seneca, the great Roman statesman and philosopher, once said: "All art is but imitation of Nature." What we try to do in science is to get ever closer to Nature.

I feel privileged to have been able to welcome you to this Congress and wish that you enjoy the science and have fun in San Francisco.

An Essay for TIBSCentenary of the Birth of Modern Biochemistry

Arthur Kornberg

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1897 was a big year for science. J. J. Thomson discovered the electron and with other momentous advances around that time ushered in the golden half-century of modern physics. It was in 1897 too that Eduard Büchner accidentally observed that a yeast juice can convert sucrose to ethanol. This discovery disposed of a firm belief that alcoholic fermentation is a vital operation of an intact cell; it was the origin of modern biochemistry. Forty years of enzyme fractionation resolved this "zymase" activity into a dozen discrete reactions. With the reconstitution of alcoholic fermentation, a phenomenon that had baffled scientists for centuries was explained in molecular terms and the stage was set for the revolutionary advances of biomedical science in the second half of our century.

During the course of resolving the alcoholic fermentation in yeast juice, glycolysis by a muscle extract was also resolved into its molecular components and astonishingly proved to be virtually identical to the yeast pathway. Conservation of mechanisms and molecules for a billion or more years in bacteria, fungi, plants and animals has since been observed in a large number of bioenergetic and biosynthetic pathways. Universality of biochemistry represents one of the great revelations of our century.

Because attention to enzymology and biochemistry has diminished in recent decades by the emergence of molecular and cellular biology, it is appropriate to be reminded of what these classic disciplines can still provide. Stated simply: (1) enzymology can solve chemical and biologic problems,

(2) biochemical resolution and reconstitution chart metabolic pathways, (3) universality of biochemistry is pervasive, (4) reverse genetics links enzymology to physiology, and (5) enzymes can be unique and powerful reagents.

(1) Enzymology solves chemical and biologic problems. Virtually all biologic operations are catalyzed, directed, and regulated by enzymes. Spontaneous reactions are rare: melting of DNA is catalyzed by multiple varieties of helicases; facile protein folding and assembly is directed by chaperonins. Enzymes are at the core of biological processes.

Chemists, previously reluctant to recognize or use enzymes, have begun to examine them for their awesome specificity and catalytic efficiency. Still remote from their attention are the social faces of enzymes, their interactions with other enzymes, structural proteins, membranes and matrices that create the functional macromolecular assemblies and organelles. Most biologists avoid enzymology. To them, enzymes are faceless components of kits or putative gene products inferred from sequences recognized only by their motifs and homologies .

(2) Biochemical resolution and reconstitution chart metabolic pathways. A biologic event must first be observed in a cell-free system in order to be resolved and reconstituted at the molecular level. In so doing, a more precise understanding of enzymes, mechanisms and pathways can be gained as can clues to their physiologic operations. Unlike the cell, constrained to provide a consensus medium for thousands of diverse reactions, the biochemist enjoys the freedom to saturate enzymes with substrates, trap products and optimize the medium for pH, metal ions, ionic strength and cofactors.

(3) Universality of biochemistry is pervasive. As an example, the replication of the genome, phages and plasmids of *E. coli* completed in a matter of minutes has proved far easier to examine than replication in organisms in which the processes take hours or days. Clearly, discoveries are more likely where the light is brighter. While recent advances in eukaryotic replication have revealed fascinating details, the basic themes and enzymes are familiar from prokaryotic systems.

(4) Reverse genetics links enzymology to physiology. Affinity chromatography and other powerful fractionation methods have enormously simplified the isolation of enzymes. Minute quantities of a near homogeneous protein are adequate for determining a short peptide sequence sufficient for identifying the gene that encodes it. Regulating expression of the gene from its knockout to overexpression leads to physiologic consequences--phenotypes--that are clues to the enzyme's functions *in vivo*. Unlike conventional genetics, in which mutants identify genes with unknown functions, reverse genetics starts with a known activity identified by classical biochemical purification.

(5) Enzymes are powerful reagents. With purification of an enzyme comes the reward of measuring a substrate quantitatively and producing a previously unobtainable pure product, isotopically labeled and in abundance. In the purification of a potato nucleotide pyrophosphatase I found novel substrates for coenzyme biosynthesis which led me to the kinases, polymerases, ligases and nucleases responsible for recombinant DNA and genetic engineering.

In my current studies of inorganic polyphosphate, novel enzymes from *E. coli* and yeast have for the first time provided definitive, rapid, sensitive assays and preparative methods. Reverse genetics applied to these

synthetic and degradative enzymes has revealed roles for polyphosphate in cellular responses to nutritional stringencies and signals essential for survival in the stationary phase.

Toward the next centenary.

The future is invented, not predicted. Forecasts of the future invariably fail to anticipate the truly revolutionary advances in the sciences and the consequent applications. In recent physics, neither the discoverers of NMR, the transistor and the laser (nor others made aware of these discoveries at the time) had the remotest conception of their applications: NMR in medicine and biochemistry; transistors in computers and communications; lasers in bar codes, CDs and surgery. In biochemistry, at the very seat of discovery of recombinant DNA in 1972, none of us anticipated the wide applications of genetic engineering to medicine, industry and basic research in biology and chemistry.

Having disavowed prediction, I will nevertheless venture some general directions for research in biomedical science.

1. Eternal vigilance to avoid vitalism. Vitalism is always about us-- sometimes revelatory, often only an excuse. Pasteur's triumphant discovery that the yeast cell is the agent of alcoholic fermentation led him, after a few failed attempts at getting an active yeast juice, to the unfortunate conclusion that the process is inseparable from a living cell. Reports to the contrary were derided and the advent of modern biochemistry was delayed for several decades. Even after the enzymatic elucidation of alcoholic fermentation, the eminent Dutch microbiologist, A. J. Kluyver, declared that fatty acid metabolism was too complex to ever be observed in a cell-free system.

The extraordinary advances in the cloning of genes and sequencing of genomes provide essential knowledge that will be of increasing and

inestimable value. These developments now beg for the biochemistry to understand the functional and organized units of the cell and organism. Just as remarkable are the techniques to knock out genes and alter the level of their expression, which provide profound insights into physiology and disease; these advances too highlight the gaps in our understanding of how these alterations produce their effects at the molecular level.

(2) Respect for chemistry as the universal language and the foundation for all the biomedical sciences. Although the cultural divide between biologists and chemists will remain, those who cultivate these neglected border areas will find the richest harvest. Chemists inspired by the vast and awesome chemistry evolved in nature will discover networks of regulated molecular operations by the use of bioassays as well as highly refined physical methods. Biologists who delve beyond physiologic phenomena and microscopic images by applying chemical techniques of ever increasing sensitivity and precision will be rewarded with a deeper understanding of biologic events.

3. Increased attention to the microbial world. Neglect of microbial research in recent decades has revealed through novel and drug-resistant microbial diseases that we, as animals, are simply guests in a microbial world. Biological and chemical studies of microbes, including those that thrive at extremes of temperature, pressure and pH, will provide, as in the past, profound insights into biochemical mechanisms, the means to avoid or combat microbial diseases, reagents for industrial processes and new approaches to improve agriculture.

4. Chemical exploration of the brain and behavior. Applications of biotechnology which have given major insights into the functions of liver, kidney and the immune system will surely be effective in explorations of the

brain. That human behavior is a matter of chemistry and neurons may be hard for some to accept, but even the modest efforts have already begun to reveal chemical explanations for mood, sleep and mental illnesses. A vast, uncharted frontier implores exploration.

When the genomes are finally sequenced, biochemistry and enzymology will be called upon to validate the gene products and account for the post-translational modifications and interactions that are at the basis of cellular function. Frederick Gowland Hopkins (1861-1947), "father of British biochemistry," founder of the Cambridge Department of Biochemistry in 1914, prescient and heroic, said of the biochemist in his Boyle Lecture in 1931: "His may not be the last word in the description of life, but without his help the last word will never be said."

Joshua Lederberg, 03:02 PM 4/18/98, Kornberg oral history -- some

1

To: (Sally Hughes)
Subject: Kornberg oral history -- some contemporary clips
Date: Sat, 18 Apr 1998 15:02:24 EDT
From: Joshua Lederberg

You might be interested in these comments. From my then weekly column

!!
77 `Creation of Life' Is More
Slogan Than a Description
The Washington Post Saturday December 23, 1967

"Creation of Life in the Test Tube" was the spectacular headline of a science news story that broke ten days ago. The occasion was a publication in the Proceeding of the National Academy of Sciences by Prof. Arthur Kornberg of Stanford's Department of Biochemistry and his colleagues, Drs. Mehran Goulian and Robert L. Sinsheimer. This reported their work on the "in vitro replication of the DNA of Phi-X-174," which is a simple virus containing only six genes.

It is just that simplicity that makes Phi-X-174 an attractive model system for genetic chemistry: higher animals, including man, would be some million times more complex. But even the simple virus has in it the imprint of eons of cosmic evolution, being one of an innumerable variety of DNA molecules that now populate the earth.

It is one of the delights of a scientific education to be able to assimilate the endless technicalities of this line of work and then appreciate the elegance and the grandeur of the thinking that went into it as well as the meticulous drudgery of preparing for the crucial experiments. The headline suggests a sudden breakthrough. In fact, Dr. Kornberg had consolidated the essential advances over 10 years with the extraction of the crucial enzyme, DNA replicase.

Since that time, the present accomplishment has been clearly in sight, though surprisingly elusive until some ancillary, but fatal gaps in scientific understanding could be filled. One of the most important of these was the action of another enzyme, a DNA "ligase," which can heal small nicks in the growing DNA standard and seal off the finishing touches on the complete molecule.

All told, the experimental replication of DNA stands as one of the outstanding intellectual edifices of the 20th century, quite apart from the philosophical and human impact of the accomplishment.

Dr. Kornberg would, however, be the first to point out that "creation of life" is a slogan rather than a thoughtful characterization: "I really don't think my colleagues and I have ever discussed whether or not this is a living molecule that we have created." To many readers, however, "creation of life" carries such a load of emotional and theologian impact that this deserves to be clarified.

Replication is an elegant way to say "copying." The propagation of life must provide for the copying of genetic information to pass similar copies to many offspring. The kernel of Dr. Kornberg's experiment was to conduct the copying of an existing virus DNA in the test tube under well-defined conditions.

The process has long been known to occur within the cell. The whole point of the experimental work is to understand how the replication process works, and this has been corroborated by being emulated in the test tube with materials extracted and purified from cells.

The leap in understanding is comparable to man's discovery that wheat could be "created" by planting the right seed in the ground. But now our understanding is at a molecular level, almost as far as human thought can be expected to reach and one that does show new ways to modify the genetic process.

If, through our understanding of DNA chemistry, we "create" new kinds of DNA molecules, we then have very powerful new tools for designing new viruses and other organisms which could be of enormous value in fighting the scourges of life. Before we react reflexly to the idea of "tampering with genes," we ought to remember that the history of human civilization runs parallel with unremitting effort at controlling biological evolution in the guise of the domestication of crop plants, animals and, in the sense, man himself.

It is in this century that we have lost the comfort of blind ignorance: we are beginning to use our intelligence to understand what we are doing.

!! spellx done

79 Replication of DNA Molecules

Shouldn't Be a Moral Issue

The Washington Post Saturday, January 6, 1968

Molecular Biology emerged from its academic sanctuary to challenge public consciousness in one of the epochal news stories of

1967 the experimental replication of virus DNA molecules.

The event was headlined by a misleading cliché, "the creation of life," and editorialized about in terms of its implications for the purposeful control of human biology. This kind of journalistic exaggeration may serve a useful purpose by attracting public attention to one of the most important scientific advances of our time. At the same time, to focus on DNA replication as an issue for moral debate is to ignore the whole thrust of scientific study of life.

These particular headlines are simply out of date. They were anticipated 140 years ago by Wohler's discovery that carbon-containing "organic" molecules, previously thought to be unique to living organisms, could be studied and synthesized in the laboratory.

The material basis of human life is shared by all terrestrial life and is based on a universal chemistry. This fact may or may not have disturbing moral implications, but it is hardly new. Prof. Kornberg's discoveries about DNA simply emphasize how true it is.

The moral issue remains unchanged: how to transcend the narrowly material aspects of man's existence represented by a body not very different from that of the lower animals.

Such a moral issue is a concern, but not a special concern, of the scientist, whether in the laboratory or as an expert consultant for public policy. He must answer a much more pragmatic challenge: to forecast and help bring about the most constructive human benefits from this new knowledge, and to educate the public and himself broadly enough to foresee the less obvious malicious side-effects.

First, it is essential to work of consolidation and further advance that lies ahead before many practical applications can be brought to fruition.

The most predictable of these is the chance to manage calculated modifications in the blueprints of existing viruses. This in turn will deepen our understanding and control of the factors that determine the capacity of a virus to cause diseases, to attack different species of host animals or to provoke immunity for protection against more serious attack.

One of the next major steps would be the actual chemical synthesis of a DNA molecule in accordance with the investigator's design. What has been accomplished so far is the replication or copying of an existing blueprint found in nature.

A further step even closer to a true creation would be the invention of new virus-like agents, still emulating the principles already displayed by naturally evolved forms. As revolutionary as this may seem, it would still be no more than a gradual extension, to the molecular level, of the domestication and intelligent breeding of wild animals and plants.

Exciting advances in this direction have come recently from the laboratory of Prof. H.G. Khorana at the University of Wisconsin. To make a viral DNA would be a thousand-fold extension of the steps he has pioneered, a task that now seems one of unachievable complexity. However, we had the same outlook about the possibility of synthesizing a protein ten years ago. By 1966, a group of Chinese chemists had accomplished the chemical synthesis of the protein, insulin.

!! spellx done

80 DNA Breakthrough Points

Way to Therapy by Virus

The Washington Post Saturday, January 13, 1968

Planning for social progress demands a vigilant search for the opportunity to link effective means with deserving goals. We are ridden with problems against which we are simply too ignorant to mount a frontal attack, for example, how to temper the ravages of aging. In such an area we must content ourselves with piecemeal advances in isolated sectors and work patiently to strengthen the whole framework of human understanding.

In the course of this process of basic research, opportunities often arise where least expected. Each should provoke the question, "What can now be done that was not possible before?" This is an opportunistic search for newly answerable problems, but in the most difficult and most important areas we have no way to program fundamental discovery.

The replication of DNA in the test tube opens the way to a number of new approaches to the study and treatment of disease. It is virtually certain that, in the long run, our mastery of cancer and of senility will be reached with the help of this stepping stone.

Meanwhile, there are some very concrete advances that we can map out with existing insights. For the moment, these would be most relevant to diseases that are connected with a hereditary defect and that have a simple biochemical basis.

The plan is founded on an unlikely combination of biological studies ranging from the genetics of bacteria to virus-induced warts in rabbits and the recent advances in molecular biology. It is a scheme that we might call "virogenic therapy." This is an extension of the already well-founded use of tempered live viruses as vaccines to stimulate immunity against their wild cousins. To see the analogy we must, however, focus on the earliest steps of a vaccination, since the later step of provoking immunity is just one special case of virogenic therapy.

In its essentials, a virus particle is a large DNA molecule protected by a protein coat. (For precision, we have to note that some viruses are RNA, but the basic principles are the same.) The DNA codes for the production of a number of special proteins related to the survival of the virus, including that coat protein but also including a number of new enzymes.

The infection of a cell by a virus is therefore tantamount to adding some new genes to that cell. The consequences depend on the specific quality of the virus as it has evolved in nature or been contrived in the laboratory. It may kill the cell and ultimately the whole animal. Alternatively, it may be essentially innocuous, adding a few additional proteins to the long list of those already synthesized by the cell.

In this context, the purpose of vaccination is seen to be to provoke the further synthesis of the virus's own coat protein. This in turn will provoke the host to develop immunity against that coat and enable the host to recognize and destroy further incursions by the same virus or its virulent cousins.

Dr. Stanfield Rogers of the Oak Ridge National Laboratories has pointed out that we should find viruses that code for other proteins needed by a giving patient, for example, insulin by a diabetic or the phenylalanine-oxidizing enzymes by a PKU-infant.

Such viruses might be found by a massive screening program to test the enormous variety of viruses that continuously evolve in nature. This kind of approach paid off very well in finding the antibiotics like streptomycin. The odds of finding an insulin-coding virus are obviously rather slim, but such a program would justify itself anyhow with its by-product of encyclopedic knowledge of virus-cell biochemistry. (That encyclopedia might one day save the humanspecies from extinction under attack by a virulent mutant of some now harmless obscure virus.)

An even more aggressive approach is based on recent work like that of Kornberg and Khorana on the enzymatic and chemical manipulation of DNA. It would be fanciful now to think of synthesizing an entire viral DNA according to our intended design, which, anyhow, we still do not know in sufficient detail. We can, however, think of extracting the DNA molecules that code, say, for insulin and chemically grafting these to the DNA of an existing tempered virus. These new hybrid viruses would then have to be very carefully studied, and perhaps modified even further, to select those appropriate for virogenic therapy in man.

This program needs to be discussed in a newspaper column as well as in scientific journals because its success is mainly a question of public policy. Existing institutions are not well suited in either style or scope to the innovative development side of "R. & D." for health.

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