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ARTHUR KORNBERG
1918–2007

A Biographical Memoir by

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Biographical Memoir

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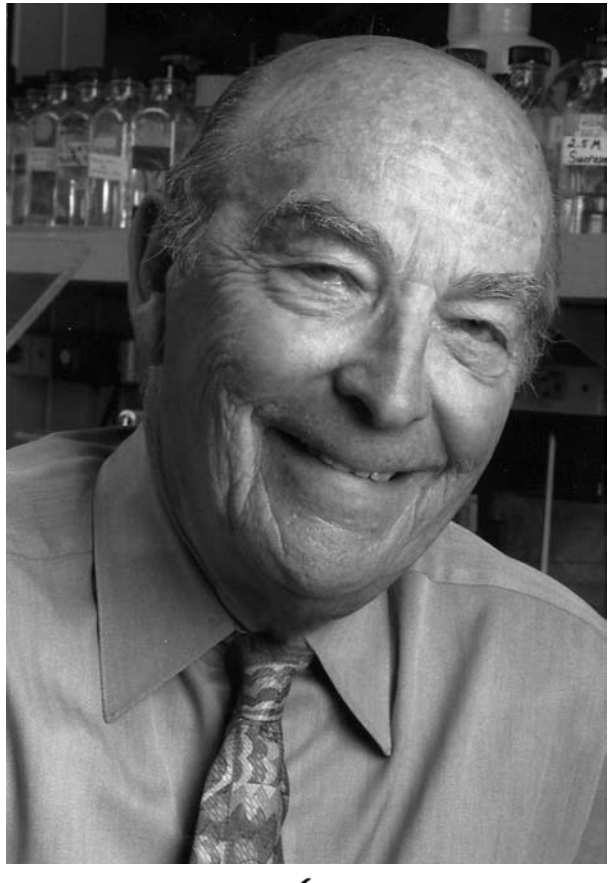

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Arthur Kornberg

ARTHUR KORNBERG

March 3, 1918–October 26, 2007

BY I. ROBERT LEHMAN

With the death of Arthur Kornberg on October 26, 2007, one of the giants of 20th-century biochemistry was lost.

Arthur Kornberg was born in Brooklyn, New York, on March 3, 1918. The son of Joseph and Lena Kornberg, both Eastern European immigrants, he grew up in Brooklyn and attended the City College of New York (CCNY), which was then—and still is—tuition free, and can count several Nobel laureates among its graduates. A precocious student, Kornberg skipped three years of school and entered CCNY at the age of 15 and graduated at 19 with a B.S. in chemistry and biology. The United States was then deep in the Great Depression, and Kornberg worked to help support the family while in high school and college, first in his parents' small hardware store and then at a men's clothing shop. With virtually no jobs to be had for a newly minted graduate of CCNY, Kornberg was fortunate in being accepted in 1937 to the University of Rochester School of Medicine, where his ambition was eventually to practice internal medicine. As a sign of the times, of the 200 premedical students in his class at CCNY only five managed to gain acceptance to a medical school.

Kornberg excelled in his medical studies. Inspired by several of the distinguished faculty at Rochester—particularly George W. Corner in anatomy and Wallace O. Fenn in physiology and prompted by self-diagnosis of his own persistent mild jaundice—he undertook a research project in which he measured his own and fellow medical students' blood bilirubin levels. The paper on his findings, which he published in the prestigious *Journal of Clinical Investigation* (1942) documented the frequent occurrence of high levels of bilirubin as a consequence of a reduced capacity to excrete it, a syndrome now recognized as a benign familial trait called Gilbert's disease.

In 1942 following a one-year medical internship at the Strong Memorial Hospital at the University of Rochester, Kornberg's ambition to practice internal medicine, took a significant detour. The U.S. participation in World War II was now at its height and he entered the U.S. Public Health Service as a commissioned officer, serving briefly as a doctor on a navy ship. As chance would have it, Kornberg's earlier publication on jaundice attracted the attention of Rolla Dyer, director of the National Institutes of Health in Bethesda, Maryland. Dyer was attempting to deal with a high incidence of jaundice among service members inoculated with the yellow fever vaccine before being deployed to the South Pacific theater of operations.

Ironically Kornberg's initial work at NIH was not on jaundice. Instead he investigated the folic acid deficiency developed by rats fed sulfa drugs. Because of Joseph Goldberger's influence, an important focus at the NIH at the time was on the role of vitamins in nutrition. Goldberger had in the 1920s recognized that the disease pellagra was caused not by a microbe, as had been largely accepted, but by a B vitamin deficiency. Nutrition research dominated by the hunt for new vitamins occupied a preeminent place in

the biochemistry of the 1920s and 1930s. However, by the mid-1940s nutrition research was in decline, replaced largely by the quest for defining the role of each of the vitamins identified in nutritional studies in intermediary metabolism. This decline was not lost on Kornberg who was enormously influenced by his reading and hearing about the advances that had been made by the great European biochemists: Otto Warburg, Otto Meyerhof, Carl and Gerti Cori, and Severo Ochoa, who had made skillful use of enzyme purification from crude cellular extracts to reconstitute *in vitro* such complex processes as glycogen breakdown and synthesis in muscle and the conversion of sugar to alcohol in yeast.

Kornberg was determined to learn the exciting new biochemistry and in 1946 he was able to persuade W. H. Sebrell, his chief at the NIH, to let him take a leave from his nutrition work and join Severo Ochoa's laboratory at the New York University Medical School for a one-year period. During this time, he married Sylvy Ruth Levy, a biochemistry student he had met at the University of Rochester and who was then working at the National Cancer Institute in Bethesda. After nearly 40 years of marriage, Sylvy Kornberg died tragically from a rare neurological disorder in 1985. Following her death he married Charlene Walsh Levering and after her death Caroline Frey Dixon, who survives him.

During the one-year period in the Ochoa laboratory, Kornberg managed to purify the malic enzyme from liver and the enzyme aconitase from muscle. Most importantly, he discovered the power (and the joy) of enzyme purification in reconstituting and thereby revealing a pathway of metabolism. This discovery was to have a profound influence on the future direction of his research. In subsequent years he was to become a passionate, almost messianic advocate for his approach in solving complex, seemingly intractable biological problems.

On Ochoa's advice Kornberg extended his one-year leave from the NIH and joined Carl and Gerti Cori's laboratory at Washington University in St. Louis for an additional six months. There he continued to immerse himself deeply in the "new" biochemistry, which further enhanced his admiration of enzymes, described in glowing detail in his autobiography, *For the Love of Enzymes* (1989). Upon his return to the NIH, with Sebrell's permission Kornberg started an Enzymes and Metabolism Section that was to include Leon Heppel, a medical school classmate assigned earlier to the NIH, and Bernard Horecker, a friend and biochemist at the NIH.

Kornberg's first research effort in the new Enzymes and Metabolism Section involved the purification and characterization of nucleotide pyrophosphatase from potatoes. This "humble enzyme," as he called it, which cleaves the pyrophosphate bond of the coenzyme NAD^+ to yield nicotinamide mononucleotide (NMN) and adenosine monophosphate (AMP), exemplified Kornberg's credo "never a dull enzyme" because it provided him with NMN, which in turn led him to the discovery of the enzyme that reversibly catalyzes the synthesis of NAD^+ from NMN and adenosine triphosphate (ATP) with the formation of inorganic pyrophosphate (PP_i)

$$NMN + ATP \rightleftharpoons NAD^+ + PP_i$$

Kornberg subsequently showed that another coenzyme, flavin adenine dinucleotide (FAD), is synthesized by a similar mechanism. Interestingly, several of the coenzymes whose synthesis Kornberg discovered were the biologically active forms of the vitamins whose nutritional role were the subject of his investigations at the beginning of his career. With his success in coenzyme biosynthesis Kornberg turned to nucleotide synthesis and discovered a key intermediate,

5-phosphoribosyl pyrophosphate (PRPP) and the reaction typified by adenosine 5' phosphate (AMP) synthesis

$$\text{Adenine} + \text{PRPP} \rightleftharpoons \text{AMP} + \text{PP}_i$$

Over the years this mechanism of nucleotide transfer together with the reversible release of PP_i was found to be a general one for the synthesis not only of coenzymes and nucleotides but also for phospholipids, peptides, and even nucleic acids. His discovery of the release of PP_i in these nucleotidyl transfer reactions was of particular importance because with an equilibrium constant near one they can be driven in the direction of synthesis by the ubiquitous presence of an efficient inorganic pyrophosphatase that hydrolyzes PP_i to inorganic orthophosphate (P_i).

Influenced by his mentors Carl and Gerti Cori, Kornberg left the NIH and moved to the Washington University School of Medicine to become chair of the Department of Microbiology. It was here that he assembled a talented young faculty, most of whom were to form the core of the Department of Biochemistry at Stanford University.

Kornberg's success in the elucidation first of coenzyme and then nucleotide synthesis reinforced the lessons learned from the work of Warburg and Meyerhoff and those practiced in the Ochoa and Cori laboratories, namely, that every biochemical process no matter how complex should be amenable to the power of biochemistry. With, as he put it, "the hammer of enzyme purification," Kornberg undertook the very formidable problem of DNA replication.

At the time (1955, two years after Watson and Crick's discovery of the double helical structure of DNA) the deoxynucleotide precursors for DNA synthesis were unknown. In fact, the Watson and Crick publication that first proposed the double helical structure of DNA and the semi-conser-

vative mode of its replication left open the possibility of a nonenzymatic replication process. Indeed, it was a matter of some speculation as to whether deoxynucleotide precursors, were polymerized to form DNA or whether the phosphate backbone structure was assembled first and the bases attached later.

Kornberg's first experiment on DNA synthesis performed in the spring of 1955 involved ^{14}C-labeled thymidine, a known constituent of DNA, that he managed to obtain from Morris Friedkin, a colleague in the Pharmacology Department at Washington University. An extract of *Escherichia coli* was chosen because of its known rapid rate of DNA replication, and DNA synthesis was measured by conversion of the acid-soluble thymidine to the acid-insoluble form when it is part of DNA. The first result of this historic experiment was rather unimpressive; approximately 50 cpm of radioactivity converted out of about a million cpm added. But, importantly, all of the acid-insoluble radioactive product was made acid soluble by treatment with crystalline pancreatic deoxyribonuclease, which had just then become available from Moses Kunitz. Presumably the thymidine substrate had formed part of a DNA molecule.

With this seemingly inauspicious beginning Kornberg and his students undertook the purification of the enzyme responsible for the conversion of thymidine to DNA by the *E. coli* extract. Over a period of approximately three years, with this simple assay to measure DNA synthesis they discovered the enzyme, which they named DNA polymerase, as well as the deoxynucleoside triphosphates (dNTPs), the substrates for the reaction. They further determined that the enzyme could not start a chain *de novo* but required a DNA primer, onto which deoxynucleotides were added by formation of a phosphodiester bond. Most importantly, they discovered that a DNA template was required, which serves to guide the

DNA polymerase in the selection of the correct dNTP for polymerization according to the Watson-Crick hypothesis. Kornberg and his students later demonstrated that although the enzyme polymerized the dNTPs in the 5' → 3' direction, it has a built-in error-correcting mechanism in the form of a 3' → 5' exonuclease, which recognized insertion of an incorrectly added nucleotide and excised it, thereby enhancing the fidelity of replication. Finally, they showed that the chemical reaction mechanism involves the nucleophilic attack of the alpha phosphorus of the incoming deoxynucleoside triphosphate on the 3' hydroxyl group at the primer terminus, with the elimination of inorganic pyrophosphate. This process is repeated sequentially until replication of the DNA template is complete.

$$\underset{\text{DNA}}{(\text{dNMP})_n} + \text{dNTP} \rightarrow \underset{\text{Extended DNA}}{(\text{dNMP})_{n+1}} \quad \begin{matrix} 2P_i \\ \uparrow \\ +\text{PPi} \end{matrix}$$

For the discovery of DNA polymerase and the demonstration that DNA synthesis by this enzyme is a template-driven process, a reaction then without precedent in biochemistry, Kornberg shared the 1959 Nobel Prize in Physiology or Medicine with his former mentor Severo Ochoa, who had demonstrated the enzymatic synthesis of polyribonucleotides by reversal of the degradative phosphorolysis catalyzed by the enzyme polynucleotide phosphorylase.

After several unsuccessful attempts to demonstrate that the DNA product of DNA polymerase was biologically active, Kornberg in collaboration with Mehran Goulian and Robert Sinsheimer was able to demonstrate the synthesis by DNA polymerase of infectious circular single-stranded bacteriophage øX174 DNA. This achievement—which involved the high-fidelity replication of a 5000-nucleotide viral chromo-

some and received wide publicity as the "creation of life in the test tube"—was aided by the discovery at the time of the enzyme DNA ligase, which catalyzes the conversion of linear to circular DNA. Very importantly, these experiments demonstrated that the DNA polymerase that Kornberg and his students purified could promote high-fidelity and complete chromosomal replication and generate biologically active DNA molecules.

It was shown subsequently that the DNA polymerase in *E. coli* (DNA polymerase I) is only one in a large class of enzymes, including five DNA polymerases in *E. coli,* DNA polymerase I, II, III, IV, and V, and 15 in eukaryotic cells. In *E. coli* the multisubunit DNA polymerase III holoenzyme is the enzyme that actually catalyzes the synthesis of the *E. coli* chromosome; DNA polymerase I plays an auxiliary role. It was a source of great satisfaction to Kornberg that DNA polymerase III was discovered by his son, Tom Kornberg, who was a biology graduate student at Columbia University, while also studying cello at the Julliard School of Music. Of the 15 DNA polymerases in eukaryotic cells most are devoted to the repair of specific lesions in DNA, and the remainder are involved in the replication of cellular chromosomes. There are in addition virally encoded DNA polymerases that replicate viral chromosomes, and in the case of retroviruses, reverse transcribe the RNA genomes into DNA. Despite their number and diversity all the DNA polymerases show the same requirements discovered by Kornberg for the first *E. coli* DNA polymerase: a template to guide the polymerase in its base selection and a primer onto which deoxynucleotides are added by nucleophilic attack from the four deoxynucleoside triphosphates. There are factors associated with DNA polymerases that increase the efficiency and fidelity of DNA replication, but the basic mechanism of replicating a DNA chain are all the same. Over the years, studies of the struc-

ture and detailed chemical mechanisms of DNA polymerases have led to a deep understanding of these enzymes. This information has been particularly valuable in the design of effective antiviral and chemotherapeutic agents.

When it became clear that DNA polymerases are not capable of starting a DNA chain, the question then became: how are DNA chains started? To address this problem Kornberg in 1970 turned to a group of homogenous single-stranded, circular DNA molecules, typified by the genomes of bacteriophages M13 and øX174. With the insight that unlike DNA polymerases, RNA polymerase does have the capacity to start a chain *de novo* without the need for a primer, Kornberg asked whether rifampicin, an RNA polymerase inhibitor, could block bacteriophage M13 DNA replication *in vivo*. The unambiguously positive result of that experiment, which was confirmed *in vitro* with cell extracts and then with purified enzymes, was that RNA polymerase initiates M13 DNA replication by forming a primer RNA for covalent attachment of the deoxyribonucleotides that start the new chain, complementary to the single-stranded M13 chromosome. Thus, the concept of RNA priming of DNA replication became a reality. Studies with øX174 DNA where replication *in vivo* was unaffected by rifampicin, led to the discovery of a specialized RNA polymerase, the DNA primase. The RNA primer is subsequently removed by the action of a specific ribonuclease activity associated with the DNA polymerase I. Over a period of about 10 years Kornberg and his students were able to identify and assemble the replisome that would convert the single-stranded circular øX174 DNA molecule to its double-stranded replicative form.

The replisome that Kornberg had assembled—consisting of proteins known from genetic studies to be essential for cellular DNA replication and could catalyze the rapid, high-fidelity replication of a small single-stranded circular

viral genome to yield a double-stranded circular DNA molecule—opened a window to the replication of the more complex chromosome of *E. coli*. However, the question still remained: How is the replication of a duplex DNA molecule initiated, propagated, and finally terminated? Solution of this problem came with the discovery of the role of another enzyme (dnaA protein), not part of the replisome, and the availability of a template consisting of a double-stranded circular plasmid DNA molecule into which the *E. coli* origin of replication had been inserted. Again using "the hammer of enzyme purification," Kornberg was able after, as he put it, "twelve man years of effort," to finally reconstitute the origin-specific replication of a duplex circular origin containing DNA molecule and thereby fully describe the replication of the much larger circular *E. coli* chromosome. As he often put it in the title of his lectures on the subject, he and his students had achieved the "replication of the *E. coli* chromosome from start to finish." This monumental achievement, clearly one of the great scientific syntheses in the history of experimental science, influenced a generation of biochemists to undertake problems seemingly beyond reach: signal transduction, intracellular protein transport, and gene expression. This last discovery culminated in the elucidation of the three-dimensional structure and the dynamics of messenger RNA synthesis by the 12-subunit eukaryotic RNA polymerase II complex by Kornberg's son Roger, who was awarded the 2006 Nobel Prize in Chemistry for this extraordinary accomplishment.

The ability to clone genes and the biological revolution that followed was in large measure possible because of the polymerases, ligases, nucleases, and related enzymes that emerged from Kornberg's work on DNA replication and similar studies carried out by people trained in the Kornberg laboratory. And of course DNA polymerase I and its many

analogues turned out to be the key reagent in the Polymerase chain reaction (PCR) and DNA sequencing upon which much of modern biotechnology is based.

Despite Kornberg's single-minded pursuit of DNA replication, he did venture into three unrelated areas: bacterial sporulation, cellular membranes, and the synthesis and biological role of polyphosphate (polyP). His studies of bacterial sporulation and germination in *Bacillus subtilis* during the period 1968-1971 were undertaken with the idea that this very simple system would allow a biochemical entrée into metazoan development. However, the rapid progress in the work on øX174 DNA replication at this time demanded his full attention, and the spore project was ultimately phased out.

Kornberg's brief entry in the early 1970s into cellular membranes followed a sabbatical leave at the MRC Laboratory in Cambridge and was prompted by the prevailing wisdom at the time that membrane attachment of the *E. coli* chromosome, and perhaps the replication machinery, was essential for chromosomal replication. This work coincided with the discovery of RNA priming of DNA replication, and for obvious reasons assumed a lower priority. However, interest in bacterial membranes returned later in the early 1990s with the discovery of the involvement of acidic phospholipids with the dnaA protein required for the initiation of DNA replication at the *E. coli* origin of DNA replication, work that is still ongoing in several laboratories.

In 1991 Kornberg returned to Poly P, a subject that had intrigued him since the 1950s when he and his first wife Sylvy Kornberg isolated an enzyme from *E. coli*, polyphosphate kinase (PPK), capable of synthesizing polyphosphate. His studies on Poly P and PPK, which as he put it, "disinterred a molecular fossil," led to the discovery of Poly P's role in bacterial growth and survival, quorum sensing, biofilm forma-

tion, virulence, and a wide variety of responses to stress and synthesis. He was convinced that future work would reveal the clinical significance of Poly P and its importance in microbial infections.

Kornberg's great influence as the father of DNA enzymology extended well beyond his scientific achievements. Equally influential was the force of his personality and his considerable expository gifts, and the ability to project his ideas as exemplified by his textbook *DNA Replication* (1992), which educated a generation of biochemists and molecular biologists. Fred Sanger conceived of the idea for dideoxy DNA sequencing while reading the chapter on DNA polymerase I in *DNA Replication*. In addition to three editions of *DNA Replication,* the last of which he coauthored with his graduate student Tania Baker, and his autobiographical *For the Love of Enzymes* Kornberg drew on his experience as a founder of the DNAX Research Institute of Molecular and Cellular Biology to author *The Golden Helix: Inside Biotech Ventures* (1995), a perceptive analysis of the biotech industry. His last book *Germ Stories* (2007), originally written for his young children and then his grandchildren, is a charming collection of poems that would reveal the wonders and dangers of the vast microbial world.

Arthur Kornberg's many contributions to science were amply recognized. In addition to the Nobel Prize in Physiology or Medicine, he was a recipient of the National Medal of Science, the Cosmos Club Award, and the Gairdner Foundation Award, among others. He was elected to membership in the National Academy of Sciences (in 1957), the American Philosophical Society, and the American Academy of Arts and Sciences. He was a foreign member of the British Royal Society and was awarded honorary doctorates from 12 universities. A new research building at the University of Rochester School of Medicine, his alma mater, bears his name.

Throughout his career Kornberg was a passionate and effective advocate for basic, untargeted research. Equally strong was his advocacy of the National Institutes of Health in which he spent his formative years as a biochemist and which he regarded as his true alma mater.

Kornberg revealed his gift as a scientific leader by first organizing the Enzymes and Metabolism Section of the National Institute of Arthritis and Metabolic Disease. He then assembled and led an outstanding Department of Microbiology at the Washington University School of Medicine, and subsequently organized the new Department of Biochemistry at the Stanford University School of Medicine. Accompanying him in the move to Stanford from Washington University were Paul Berg, Melvin Cohn, Dave Hogness, Dale Kaiser, and the author of this memoir, and Robert Baldwin from the University of Wisconsin. It is indeed a tribute to his leadership that of the six faculty members who accompanied him from St. Louis to Stanford in 1959, five have remained at Stanford to this day and have achieved national and international recognition.

An unusual and much admired arrangement that Kornberg initiated at Washington University and maintained at Stanford was the mixing of the department's graduate students and postdoctoral fellows so that general biochemistry space was shared by all members of the department. This arrangement maximized interaction and collaboration between the various research groups, which was particularly important for promoting discoveries by the various research groups and sharing of critical reagents and new methods. This practice greatly facilitated the origin and development of recombinant DNA technology at Stanford. Such an arrangement, which regrettably does not seem to have been adopted very often elsewhere, obviously requires relatively small research groups in order to succeed, and indeed Kornberg set the standard

by maintaining a research group of never more than a dozen, even during periods of his greatest productivity.

Perhaps Arthur Kornberg's greatest legacy, and the one of which he was undoubtedly most proud, was his extraordinary family of three sons and eight grandchildren. His sons are Roger Kornberg, a professor of structural biology at Stanford and winner of the 2006 Nobel Prize in Chemistry; Thomas Kornberg, professor and vice chair of biochemistry and biophysics at the University of California, San Francisco; and Kenneth Kornberg, founder of Kornberg Associates, an architectural firm that specializes in laboratory design.

On a personal note, I was very fortunate to have been a postdoctoral fellow with Arthur in the mid 1950s when the DNA polymerase was discovered. I still view those days to be among the most thrilling and enjoyable of my scientific career. There were new and unexpected findings being made virtually every day and all of us in our small group—consisting in addition to Arthur, of myself and Maurice Bessman, postdoctoral fellows, and Ernie Simms, Arthur's devoted research assistant, and his wife, Sylvy Kornberg—shared in the joy and excitement of these discoveries.

Arthur's style of doing science, his demand for excellence, his absolute intolerance of mediocrity, and his perseverance inspired those of us who worked with him. He was an absolutely superb teacher. But more than that, he was a generous and compassionate mentor, devoted to his students and colleagues and fiercely loyal to his family and friends. He will be greatly missed.

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