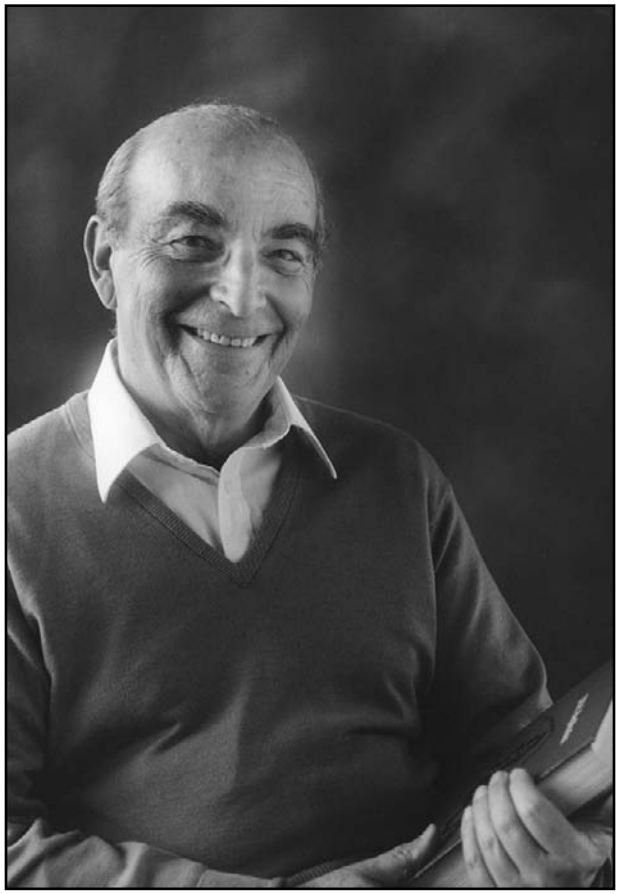
ARTHUR KORNBERG



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ARTHUR KORNBERG, one of the greatest biochemists of the twentieth century, died on 26 October 2007 surrounded by his wife, three sons, and their families. Those students and colleagues whose lives he touched and influenced will forever treasure his memory.

In his autobiography, *For the Love of Enzymes*, Kornberg confessed to a lifelong love affair with enzymes and a dedicated reliance on what he called the "hammer of enzyme purification" to probe the intricacies of biochemical systems. He exploited that approach brilliantly in his investigations of coenzyme, phospholipid, and nucleotide biosynthesis. Confident that the synthesis of very complex biological molecules could be analyzed by isolating the enzymes responsible for each step in the process, he undertook and solved the very formidable complexities of DNA replication. It stands as a monumental achievement in the pantheon of biological discoveries.

Kornberg was born in Brooklyn, New York, on 3 March 1918, the son of parents who had emigrated from Eastern Europe and ran a small hardware store. He graduated from high school at age fifteen and entered the City College of New York, where he majored in chemistry and biology. With the nation mired in the depths of the Depression, he recognized that his scientific training could be the underpinning for a career in medicine, and he enrolled in the University of Rochester's medical school to become a physician. He excelled in his studies there and found time to conduct an independent research project focusing on his own predisposition to jaundice. He sampled his own and fellow students' bilirubin blood levels and determined that there was considerable variation not only in the daily levels but also in the way those levels were regulated after an injection of bilirubin.

After he received an M.D. in 1941, Kornberg's ambitions to become an "internist with academic connections" were thwarted by the necessities of the nation's entry into World War II. Accordingly, he entered the U.S. Public Health Service as a ship's doctor in the U.S. Coast Guard. Partly because he and the ship's captain agreed that he was ill-suited for sea duty and because his early research was so promising and relevant to the military's concerns about jaundice associated with yellow fever, he was transferred to the National Institutes of Health (NIH), where he was assigned to a group that was studying nutrition.

For a time, Kornberg enjoyed experimenting with rats and appreciated the freedom from the restrictions of carrying out such research with humans. The growing awareness of the importance of vitamins for human health led him to investigate why rats fed sulfa drugs developed a vitamin deficiency. That work led to his discovery of the nutritional requirement for folic acid. However, after several years, feeding

and weighing rats on different diets and keeping track of which ones died and lived failed to quench his far-ranging investigative instincts. He was clearly finding less interest in keeping track of what animals ingested and what came out than in learning what was happening in between.

Kornberg and a small group of colleagues were becoming increasingly aware of and excited by the advances that had been made by the great biochemists of the 1930s and 1940s: F. G. Hopkins, Otto Warburg, Otto Meyerhoff. Their work revealed that by using the power of enzyme purification it was possible to reconstitute the seemingly most complex physiological processes. Thus, in an increasing number of instances, complex biochemical processes such as glycogen breakdown and resynthesis in muscle, and the conversion of sugars to alcohol, could be recapitulated in muscle or yeast extracts, respectively. Furthermore, many of the reactions involved in these processes could be carried out with isolated enzymes.

Soon after the war ended, Kornberg prevailed on his supervisor and the director of the NIH to grant him leave during 1947 to gain experience in enzymology. That year was pivotal for personal and scientific reasons. Soon after moving to Bethesda, he renewed an acquaintance with Sylvy Ruth Levy, a biochemistry student he met at the university in Rochester, who was working at the National Cancer Institute. They married in 1947, and she and Arthur worked together during the six years at Washington University and briefly after the move to Stanford. Her life ended tragically as a result of a neurological disorder in 1986.

Kornberg's ambition to gain hands-on experience with enzymes attracted him to Severo Ochoa, a Spanish émigré whose extensive experience in leading European biochemistry laboratories had made him a legend in biochemistry. Although he failed during the year to obtain the enzyme he had set out to purify, he was inspired by Ochoa and those with whom he shared the long days and nights at the lab bench. Ochoa encouraged him to spend an additional six months with Carl and Gerty Cori at Washington University in St. Louis, Missouri. The Coris, natives of Prague who had emigrated in 1922, were generally regarded as America's leading biochemists and shared the 1947 Nobel Prize in Physiology or Medicine. The six months with the Coris and the year before with Ochoa imbued him with a passion for biochemistry and enzymes that he never lost. Moreover, the Kornbergs, Ochoas, and Coris became lifelong friends and confidantes. In his later years, Kornberg acknowledged his deep indebtedness to Ochoa and to Carl and Gerty Cori in an essay, "Remembering Our Teachers."

Following his return to the NIH he identified the enzymes and reaction mechanisms for the synthesis of several important co-enzymes that

function in a diversity of biochemical pathways; interestingly, most of the co-enzymes are the biologically active forms of the vitamins whose nutritional role he had been investigating. During those studies he and his wife discovered the biological existence of inorganic pyrophosphate and a polymeric form of inorganic phosphate, each of which would occupy his attention for much of the latter part of his life. As the forerunner of his major works on nucleic acids, he undertook to discover how nucleotides, the building blocks of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) are synthesized. In that study, he discovered that the biosynthetic precursors of purines and pyrimidines condense with a novel and reactive derivative of ribose, 5-phospho-1-ribosylpyrophosphate.

In 1953, the biological world was stunned by the discovery of the molecular structure of DNA. The Watson-Crick model proposed a bihelical structure in which two polydeoxynucleotide chains are wound around each other, the two chains being held together by hydrogen bonds between opposing purines and pyrimidines. The particular order of purine-pyrimidine pairs along the double helical length was deemed to represent the genetic information that informs an organism's nature. While DNA from virtually all organisms has the same molecular structure, the order of purine-pyrimidine pairs is unique to the species. Replication, Watson and Crick proposed, occurred by transient separation of the two chains and the assembly of new chains by restoring the identical purine-pyrimidine pairs of the parental molecule. The challenge to discover how this occurs in detail, particularly the nature of the enzymes involved in such a complex process, was a tempting target for Kornberg.

In painstaking fashion, with only the barest hint that he was measuring DNA synthesis, Kornberg and his colleagues isolated a pure DNA polymerase from the bacterium *Escherichia coli*, the first enzyme capable of incorporating nucleotides into a DNA molecule. The availability of the purified enzyme enabled him to establish that DNA synthesis proceeds by stepwise addition of the nucleotidyl residues from nucleoside triphosphates to the 3′ end of an existing DNA chain. What was most important, the order of nucleotide addition relies on pairing between a newly added purine or pyrimidine nucleotide with its complementary pyrimidine or purine on a DNA template. Significantly, the enzyme copies the template in the 3′-to-5′ direction and new chain elongation occurs in the 5′-3′ direction, all features that were consistent with the presumptions in the Watson-Crick model of the DNA double helix.

The sheer brilliance of Kornberg's achievements and the fundamental importance of his discovery that the synthesis of new DNA chains depends on copying an existing DNA chain were rewarded only a few

years later with the 1959 Nobel Prize in Physiology or Medicine. Sharing the prize with Severo Ochoa, who was recognized for his discovery of a novel synthesis of RNA, was especially gratifying.

Further study of the pure DNA polymerase disclosed that it possessed additional activities: nucleases that can degrade the strands in double-stranded DNA in the 5′-3′ direction and a separate activity to degrade single-stranded DNA from its end in the 3′-5′ direction. The 5′-3′ nucleolytic activity proved to be essential for the participation of DNA polymerase in the repair of damaged DNA and the 3′-5′ exonuclease ensures the high fidelity of nucleotide addition by facilitating the removal of mismatched purines or pyrimidines. Seeking to establish that DNA polymerase is capable of producing biologically relevant DNA, Kornberg and his students set out to synthesize, *de novo*, a biologically active copy of the single-strand DNA chromosome of an infectious bacteriophage ϕX 174. Many in the media hailed that accomplishment, literally, as the creation of life in the test tube. But Kornberg saw it as confirmation that DNA polymerase could faithfully copy a mini DNA chromosome of about 5,000 nucleotides with all the biological properties of the original chromosome.

Unfazed by that success, Kornberg's laboratory proceeded to reconstitute the exceedingly complex process of bacterial chromosome replication in vitro. The key breakthrough was the discovery that replication is initiated by specialized primase proteins acting at specific sites on the DNA chromosome to permit the synthesis of short RNA molecules that act as primers from which new DNA chains are elongated. Whereas the DNA polymerase discovered earlier was found to be primarily concerned with the repair of damaged DNA, a different DNA polymerase is required for replicating double-stranded DNA. That enzyme together with a complex array of purified accessory proteins serves to initiate and complete the replication of an entire bacterial chromosome in vitro. That research revealed that during replication of the chromosomal double helix the two new DNA chains are synthesized, simultaneously but in opposite directions. It is ironic that the DNA polymerase specifically involved in chromosomal replication was discovered by Tom Kornberg while he was working at Columbia University as a respite from his studies at the Juilliard School of Music.

That monumental achievement influenced a generation of biochemists to undertake problems as seemingly intractable as gene expression, signal transduction, intracellular protein transport, and many others. The ability to clone, amplify, and sequence genes that constitutes the "biological revolution" followed in large measure from the identification and purification of polymerases, ligases, nucleases, and related enzymes that emerged from these studies.

In the early 1990s Kornberg turned from the work on DNA replication to the study of the origins and biological function of inorganic polyphosphate, poly P, a subject that had intrigued him since the 1950s, when he and his first wife, Sylvy, had isolated polyphosphate kinase (PPK), an enzyme that synthesized poly P. His studies of 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 formation, virulence, and a wide variety of responses to stress and stringencies. He was convinced that future work would reveal the clinical significance of poly P and its importance in microbial infections.

Kornberg's personality, his considerable expository gifts, and his ability to project his ideas are exemplified by his superb textbook *DNA Replication*, which educated a generation of molecular biologists. Fred Sanger conceived of the idea for the "dideoxy" DNA sequencing method while reading the chapter on DNA polymerase I in *DNA Replication*. In addition to three editions of *DNA Replication* and *For the Love of Enzymes*, Arthur drew on his experience as a founder of the DNAX Research Institute of Molecular and Cellular Biology to write *The Golden Helix: Inside Biotech Ventures*. His last book, the just-published *Germ Stories*, is a collection of poems originally written for his children and then his grandchildren that would reveal the wonders and hazards of the microbial world.

Kornberg's influence extends well beyond his scientific achievements. The microbiology department he founded at Washington University, St. Louis, Missouri, in 1953 and the biochemistry department at Stanford University founded six years later were organized along lines that were novel at the time and remain so at most institutions today. The overriding theme was communality, the sharing by the faculty of space, equipment, and funding. Above all there was an acceptance of a culture of openness and shared excitement about each other's research. Although faculty members carried out their own research programs, members of their research groups were distributed throughout the department's laboratories. Indeed, all lab facilities were deemed to be departmental. Consequently any one lab could be populated with graduate students and postdocs from different research groups, the composition changing with time as people left and arrived. Students came to acknowledge that they benefited more from having lab mates who provided a broad exposure to the department's ongoing activities, than they would have from exposure only to members of their own research groups. The principal benefit of this kind of organization was the rapidity with which news of novel discoveries and ideas, research advances, and the availability of new tools and reagents diffused through the

department. Over the years, important research collaborations and breakthroughs could be traced to the interactions of students working in close proximity. The commitment to share research space also contributed to a self-regulated commitment to maintain small research groups, which in turn enabled the relatively small faculty to interact with each other and to keep abreast of the progress of each of the graduate students in the department.

Kornberg was a keen judge of people. The scientists he recruited to join him in St. Louis formed the nucleus of the department he created at Stanford. At the time of his death, all but one of the seven founding faculty members of the department remained at Stanford, a tribute to his leadership. The sense of shared ownership he fostered among his colleagues enabled them to assume leadership roles in the department and in the university.

Kornberg's contributions to science did not go unrecognized. In addition to the Nobel Prize, he was a recipient of the National Medal of Science, the Cosmos Club Award, and the Gairdner Foundation Award, among many others. He served as president of the American Society of Biological Chemists and was elected to membership in the United States National Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society, and was a foreign member of the British Royal Society. He was an enthusiastic supporter of the Weizmann Institute, visiting whenever he could, and was a member of its Board of Governors for many years. He was also awarded honorary doctorates from twelve universities. As an unabashed and fervent admirer of the National Institutes of Health (NIH), he frequently lectured the Congress and the administration about the critical role of basic biomedical research in medicine.

Nothing surpassed Kornberg's devotion and love for his three sons. Each has achieved success in a chosen field related to science: Roger, a professor of structural biology at Stanford, was the winner of the 2006 Nobel Prize in Chemistry for his discovery of the structure and mechanism of RNA polymerase; Thomas Kornberg is an accomplished developmental biologist, a gifted cellist, and professor of biochemistry and biophysics at the University of California, San Francisco; Kenneth Kornberg is the founder of Kornberg Associates, an architectural firm that specializes in laboratory design.

He spent many hours sharing his love of science with his daughters-in-law and his eight adoring grandchildren. Following the death of Sylvy in 1986, he married Charlene Walsh Levering. After her death in 1995, he married Caroline Frey Dixon.

Aside from his magnificent scientific achievements, his legacy resides with the many students and colleagues with whom he shared his life.

He was unfailingly concerned about the welfare of his students, his colleagues, and his friends. He treasured greatly the opportunities to visit with many of them during his extensive travels at home and abroad.

Here are some remembrances:

> Working with Arthur was not always easy but it was always rewarding. The most enduring memories, though, were learning from Arthur to respect science as a search for the uncompromising truth and to perceive that search to be inherently valuable. *Bob Fuller*

> The most amazing thing about Arthur's lab is that, although he was tough on us, he believed in us and in our ability to solve problems, learn new things and succeed. *Tania Baker*

> Arthur not only taught science, he was an incredible human too, and taught many things about life. *Michael O'Donnell*

> Arthur demanded much from others as well as from himself, but he also gave of himself to those of us who were lucky enough to have known him. *Boyana Konforti*

> . . . by recruiting people that were smarter than he was, and by helping his colleagues do better research, he was creating conditions in which his own research would flourish. *Ron Davis*

> Arthur had no patience for emotionality. In the face of failure his response was that you learn more from success than from failure. *Lee Rowen*

> Arthur was much more than a scientist. . . . He was a warm and caring human being, with a special charm. *Jim Spudich*

> He brought people together with remarkable effectiveness and, by exemplifying hard work and high standards, was able to solve problems of great complexity with elegance. *Charles Brenner*

> They don't come any better than Arthur! *Charles Yanofsky*

My own relationship with Arthur Kornberg went beyond that of a student and mentor. Soon after I joined his lab as a postdoc, my wife and I were embraced as members of his family and we shared many of the special occasions and achievements they celebrated. Even though I already had a problem in mind to work on when I joined his lab, he encouraged me to give it a try and throughout he was eager to hear about my progress and quick with encouragement when things were not going well. Over the course of time, close friendship took the place of mentorship, and discussions about art, music, and politics filled in times when our discussions about experiments lagged. That was particularly the case during our travels together one summer in Vancouver, British Columbia, where, besides getting some essential research done, we hunted for

salmon and gold, neither successfully. There were also extensive travels in Spain for the Spanish government's tribute to Severo Ochoa, and on to Paris for the wedding of one of his students. Throughout the trip Kornberg was relaxed, adventurous, funny, and occasionally bawdy.

The closeness of our relationship may have stemmed from our shared heritage as sons of immigrants, growing up in Brooklyn not very far from each other and attending the same high school. More likely, it was our shared passion for and commitment to research and the great pleasure we experienced both in doing and in talking about our own experiments and those of others. In our seminars, we often had vigorous debates about different approaches to solving problems, all to the delight of the students who watched us argue heatedly our respective preferences. When, after a time, I decided to forego continuing my enzymological studies of protein synthesis in favor of initiating the molecular genetic analysis of mammalian tumor viruses, his heartfelt concern was that I was putting my career in jeopardy. But when that work flourished, he was up front with his praise. And when I took on the leadership of the department he founded, his experience and support were there when I needed them. Arthur Kornberg was the most influential person in my scientific career, and, most assuredly, many of the values I hold and actions I took over the years reflected what I had absorbed during our association of nearly fifty-five years.

Elected 1960

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