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Arthur Kornberg (1918–2007): A Man of More Than Just Two Cultures

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Arthur Kornberg, Professor of Biochemistry at Stanford University and one of the most important and influential scientists of the 20th century, died October 26 of respiratory failure. He had been at work only two days earlier in his office at Stanford University Medical Center. He was 89.

The facts of his life are well-known and easily accessible in his engagingly personal survey of the history of biochemistry and memoir *For the Love of Enzymes*, published in 1989 (*1*). Arthur was born March 3, 1918, in Brooklyn, the son of Eastern European Jewish immigrants. He grew up in Brooklyn, graduating from Abraham Lincoln High School. He graduated from the City College of New York with a B.S. in chemistry and biology in 1937 at the age of 19, and he earned his M.D. from the University of Rochester in 1941. During his time at Rochester, he published his first paper, in the *Journal of Clinical Investigation*, on prevalence of defects in bilirubin catabolism, work that began with a self-diagnosis of his own mild but chronic jaundice (Gilbert's syndrome). Following his internship, Arthur became a commissioned officer of the U.S. Public Health Service. After a brief interlude as a ship's doctor for the Navy, he was recruited to the National Institutes of Health (NIH) by the director, Rolla Dyer, who had noticed his bilirubin paper. It was here that his research career began.

Arthur joined the NIH in the waning days of the "vitamin hunters", but soon made a jump to enzymology, becoming, as he referred to it, one of the "enzyme hunters". His early work in enzymology, training with Bernard Horecker at the NIH, with Severo Ochoa at New York University in 1946, and with Carl and Gerty Cori at Washington University Medical School in 1947, focused on reactions involved in oxidative synthesis of ATP, for which Ochoa had recently coined the term "oxidative phosphorylation". The search for *soluble* enzymes responsible for aerobic synthesis of ATP was fruitless for reasons now obvious, but the training received was key to Arthur's establishing a laboratory of enzymology at the NIH in 1948 and served as an inspiration throughout his career. The Coris were to receive the Nobel Prize in Physiology or Medicine that very year for their work on glycogen enzymology and Ochoa was to share the 1959 Nobel Prize in Physiology or Medicine with Kornberg.

It was after his sojourns with Ochoa and the Coris that Kornberg began studies of the metabolism of nucleotide coenzymes that led to his appreciation of phosphoryl group transfer reactions. Knowledge of such reactions was essential to his later appreciation of the reactions of ribo- and deoxyribonucleotide synthesis, which in turn led to his groundbreaking studies of the enzymatic synthesis of DNA and DNA replication, the work for which he is best known. A key discovery at this time was the synthesis of NAD^+ from nicotinamide ribose phosphate and ATP with the release of the β- and γ-phosphates of ATP as inorganic pyrophosphate, catalyzed by NMN adenylyl trans-

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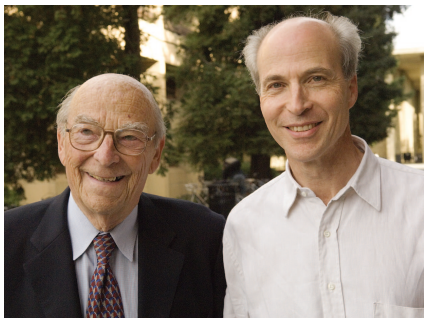


Arthur and Roger Kornberg, October 4, 2006, after Roger received notification of the 2006 Nobel Prize for Chemistry. Image by Linda A. Cicero/Stanford University News Service.

ferase. Pyrophosphate release from a nucleoside triphosphate is a common theme of synthetic reactions where the nucleophile may be a lipid (phosphatidic acid), a sugar, an amino acid, or the 3′OH primer terminus of a replicating strand of DNA. A prolific period followed during which Kornberg and his colleagues made key findings on *de novo* pathways of pyrimidine biosynthesis and discovered the salvage pathways of nucleotide biosynthesis and their reliance on a novel precursor, 5-phophoribosyl-α-pyrophosphate.

During this time, Arthur moved to Washington University to head the department of microbiology. It was here where he began to assemble a talented, young faculty, part of which would form the core of the Department of Biochemistry he would establish at Stanford University.

In St. Louis, Arthur first detected DNA synthesis in extracts of *Escherichia coli* and, together with postdoctoral fellows Bob Lehman and Maurice Bessman and others, purified and analyzed the responsible enzyme, now known as DNA polymerase I. This work, initially rejected by the *Journal of Biological Chemistry* (take heart, young investigators!), was published in the journal in 1958. Now ~50 years later, the importance and impact of this and the follow-on work cannot be overstated. Kornberg, Lehman, and colleagues did not merely purify an enzyme, they established all of the fundamental chemical paradigms for polynucleotide biosynthesis that are conserved in all life on Earth: template dependence in compliance with Chargaff's rules, primer dependence (for DNA polymerases), dependence on nucleoside 5′-triphosphate substrates, synthesis in the 5′−3′ direction with release of pyrophosphate, fidelity (achieved through both base selection and editing by a 3′5′ exonuclease activity), and processivity. All of this depended on Kornberg's prior elucidation, with Irving Lieberman, of the enzymatic synthesis of ribonucleoside triphosphates. More broadly, Kornberg's work founded the field of nucleic acid enzymology, an area of research now so vast and important that it touches and informs a bewildering array of human endeavors, from medicine and pharmaceutics to forensics and agriculture. DNA polymerase is the workhorse enzyme that sequenced the human genome and many dozens of others, and it is the engine of polymerase chain reaction. For the discovery of enzymatic synthesis of DNA, Arthur Kornberg was awarded the 1959 Nobel Prize in Physiology or Medicine together with his former mentor, Severo Ochoa, who had identified enzymatic synthesis of RNA by reversal of the degradative phosphorolysis of RNA by polynucleotide phosphorylase.

Also in 1959, Kornberg moved to Palo Alto as chairman of a new Department of Biochemistry at Stanford Medical School and brought with him several of his Washington University faculty, former postdocs Lehman and Paul Berg, who would receive the 1980 Nobel Prize in Chemistry for recombinant DNA research, along with biochemists David Hogness and Melvin Cohn (who later moved to the Salk Institute), and phage geneticist Dale Kaiser. They were soon joined by Buzz Baldwin, a physical biochemist, completing a formidable core group of researchers with diverse skills in chemistry, biochemistry, genetics, and biophysics, who were committed to employing simple model systems (at the time, bacteria and their viruses) and, importantly, who communicated with one another freely, sharing space, resources, reagents, and ideas. The creation of this remarkable institution, which has trained hundreds upon hundreds of students, postdoctoral fellows, and visiting faculty, must rank as one of Arthur's great accomplishments. The department will celebrate its 50th anniversary in the summer of 2008 in Arthur's honor.

Kornberg's laboratory continued studying the activities of DNA polymerases at Stanford. In the 1960s, he made forays into studies of *Bacillus* spore formation and germination as a synchronized model for cell division, but it was the incipient studies of the small bacteriophage M13 and ΦX174, with their single-stranded, circular genomes, that led Kornberg from studying DNA synthesis to DNA replication, the more complex process whereby genomes of viruses and cells are duplicated. From the early 1970s into the 1980s, Kornberg's laboratory elucidated the enzymatic machinery required to replicate these viral chromosomes, first by synthesis of a complete, circular strand complementary to the viral single-stranded circle and then by creation of new viral circles from the intermediate, double-stranded "replicative form" through a rolling-circle mechanism. All but one of the enzymes andproteins required to reconstitute these reactions were found to be encoded by the host bacterium and to function in one way or another in replication of the bacterial chromosome. Key concepts of general importance that were elucidated through this work were (i) the role of a complex, accurate, and highly processive replicative polymerase, the DNA Polymerase III (Pol III) holoenzyme; (ii) a "primosome" complex, containing among other components a specialized RNA polymerase (DnaG), termed DNA primase, required to synthesize RNA primers, and an ATP-hydrolysis dependent DNA helicase (DnaB), required both at the replication fork for unwinding

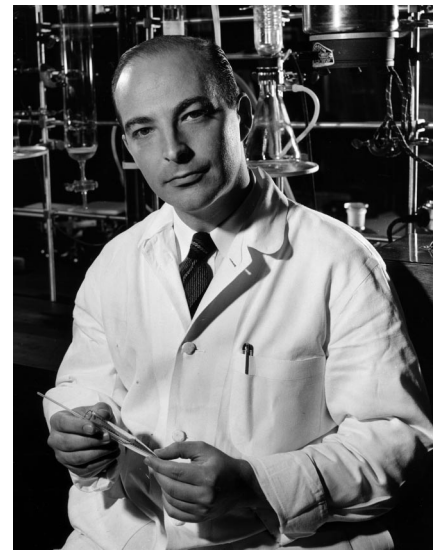
DNA and as the motor for moving the primase along the template to deposit the occasional primers required for synthesis of the discontinuous or lagging strand; and (iii) a single-strand DNA binding protein needed to melt secondary structure in the template and facilitate rapid polymerase action. In the 1980s and early 1990s, Kornberg and his group took the study of chromosomal replication one step further with the reconstitution of initiation of bidirectional replication at the origin of the *E. coli* chromosome, *oriC*. These studies demonstrated the complex roles of the "replicon-specific" factor, the DnaA ATPase, in specific recognition of the 245 base pair origin sequence, melting of the duplex DNA to reveal single-stranded template and recruitment of the rest of the replication machinery—the primosome and Pol III holoenzyme.

In something of a surprise move in 1993, Arthur refocused the work in his laboratory from DNA replication onto an old problem, the enzymology and physiological significance of the ubiquitous polymer polyphosphate, which he had worked on many years previously with his wife, the accomplished biochemist Sylvy Kornberg. Kornberg and his laboratory continued productive studies of the biology and biochemistry of polyphosphate right up until his death.

Arthur and Sylvy were married for 43 years up to her death in 1986. In the early days, they worked together in laboratory. They had three sons, Roger, Professor of Structural Biology at Stanford and recipient of the 2006 Nobel Prize in Chemistry for elucidation of the 3D structure of eukaryotic RNA polymerase II; Tom, Professor of Biochemistry and Biophysics at the University of California, San Francisco, who studies cell fate determination in *Drosophila* development; and Ken, a successful architect whose firm specializes in the construction of laboratories and laboratory buildings. Arthur was married in 1988 to Charlene Levering, a talented scientific illustrator, until her death in 1995. He is survived by his third wife, Carolyn Dixon, whom he married in 1998.

This is a highly appropriate place to review the contributions of Arthur Kornberg to science, because, as it happens, he was quite passionate about both chemistry and biology, the dual subjects of this journal. In 1987, he published an article in *Biochemistry* entitled "The Two Cultures: Chemistry and Biology" (*2*), a play on the 1959 essay by C. P. Snow that had bemoaned the lack of communication between scientists and "literary intellectuals" (*3*). Kornberg addressed both the strengths and weaknesses of chemistry and biology as disciplines in tackling the understanding of life at the molecular level, the difficulties in communication between the chemists and biologists, and the failure, as he saw it, of biochemists to bridge the gap. The remedy he proposed mirrored his own philosophy of research; that is, for all concerned to become less parochial and to appreciate and learn to use the powerful methods and ways of thinking of the other disciplines. To some extent, biological sciences have gone in this direction. It is essential nowadays for investigators to use all possible means to understand problems. In particular, chemical biology was created as a way to infuse, intelligently, the power of synthetic chemistry into studies of important biological systems.

Arthur Kornberg was a devotee of the cultures of both chemistry and biology, and he built his department and conducted his own research in a broadly multidisciplinary fashion. But he was a resident of other cultures as well. He was a prolific and accomplished writer, with an economical and engaging style. In addition to his several hundred peer-reviewed papers and countless review articles, he wrote books on DNA synthesis and DNA replication, he wrote the aforementioned memoir on his love affair with enzymes, and he wrote about the development of the biotechnology industry. His 1992 second edition of *DNA Replication*, cowritten with former student Tania Baker,



Arthur Kornberg in his lab, 1959. Image from NIH/US Government.

is as authoritative a scientific monograph as one will find. He could also blend wit with information. If the science-related careers of all three of his sons seem surprising, perhaps it was the result of the "germ stories" he told them when they were young. His children's book, *Germ Stories*, which recounts "the parade of the strangest creatures ever made", has just been published by University Science Books (*4*).

Beyond the university, he was also active in the culture of the biotechnology industry, both as a founder of the DNAX Research Institute and as a member of the scientific boards or directorates of several biotechnology companies. He was an enthusiastic member of the culture of scientific advocacy, to which he contributed through many opinion pieces, lectures, and appearance before congressional panels. In particular, he was an advocate of the importance of science as an avenue simply to understanding nature, an atypical point of view in the current times, when funding agencies threaten to favor translational over basic research. He was an equally avid advocate of chemical reductionism in biology and of understanding mechanism, even as

the fashion has now turned more to the search for correlations within huge biological data sets. There is, of course, no doubt that applied research is important and that genomics and proteomics provide invaluable and novel information about complex biological systems, but Arthur might simply assert that there will be little discovery of new information without the truly basic study of nature at a mechanistic level. He was a tireless advocate of the NIH, which he called his "alma mater". He was a particularly strong advocate of NIH funding of basic, investigator-initiated research that utilizes the simplest model systems to shed light on the most important, basic problems. The value and success of this approach is unmistakable in the impact on biomedicine of the NIH-funded research on the nucleic acid enzymology of *E. coli* and its viruses.

Finally, Arthur Kornberg was a leader in the culture of teaching. He was an innovator in medical education at Stanford, and he was a challenging, sometimes intimidating, but, ultimately, tremendously inspiring mentor to the dozens of students and fellows like me who were fortunate enough to train in his laboratory. He will live on at our side, sometimes perhaps peering over our shoulders, and certainly, if we are successful, in the students and fellows whom we train.

To learn more, visit "The Arthur Kornberg Papers" at the *Profiles in Science* site of the National Library of Medicine (http://profiles.nlm.nih.gov/WH). This is a virtual archive of key papers, documents, and correspondence, along with brief historical overviews, that will give the reader personal insights into the discoveries and scientific career of a remarkable man.

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