Review

Historical perspective: Arthur Kornberg, a giant of 20th century biochemistry

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For physics, the period from the beginning to the middle of the 20th century was one of great scientific excitement and revolutionary discovery. The analogous era for biochemistry, and its offspring, molecular biology, was the second half of the 20th century. One of the most important and influential leaders of this scientific revolution was Arthur Kornberg. The DNA polymerase, which he discovered in 1955 and showed to have the remarkable capacity to catalyze the template-directed synthesis of DNA, contributed in major ways to the present-day understanding of how DNA is replicated and repaired, and how it is transcribed. The discovery of DNA polymerase also permitted the development of PCR and DNA sequencing, upon which much of modern biotechnology is based. Kornberg's studies of DNA replication, which spanned a period of nearly 30 years, culminated in a detailed biochemical description of the mechanism by which a chromosome is replicated. The final years of Kornberg's life were devoted to the study of polyphosphate, which he was convinced had a crucial role in cellular function.

Early years

Arthur Kornberg (Figure 1) was one of the greatest biochemists of the 20th century. Despite the enormous impact of his work, Kornberg's entry into the field of biochemistry was serendipitous. The son of Eastern European Jews, he grew up in Brooklyn and attended the City College of New York (CCNY; NY, USA), notable for the excellence of its students (several of whom were to eventually receive the Nobel Prize) and for being tuition free. Having 'skipped' three years in high school, Kornberg entered CCNY at the age of 15 and graduated at 19 in 1937 with a BS in Chemistry and Biology. The USA was still deep in the Great Depression during this time and Kornberg worked to help support the family while attending college, first in his parents' small hardware store and then at a men's haberdashery. With almost no jobs to be had for a newly minted graduate of CCNY, Kornberg was fortunate in being accepted into the University of Rochester School of Medicine (NY, USA), where his ambition was to practice internal medicine. Although research held some interest for him, he was denied several of the research fellowships offered at the University of Rochester, very likely because of religious barriers that were prevalent in American Medicine in the 1930s. Nonetheless, Kornberg undertook a research project on his own initiative. Prompted by self-diagnosis of his own mild jaundice, he made similar measurements on fellow medical students and patients, first as a medical student and then as a medical intern. The paper that he published in the *Journal of Clinical Investigation* [1] documented the frequent occurrence of high bilirubin levels as a consequence of a reduced capacity to excrete it, a syndrome now recognized as a benign familial trait called Gilbert's syndrome. Following a one-year internship from 1941–1942 at the Strong Memorial Hospital at the University of Rochester, Kornberg became a commissioned officer in the US Public Health Service (www.usphs.gov) and served briefly as a doctor on a Navy ship. His publication on jaundice attracted the attention of Rolla Dyer, the Director of the National Institute of Health (NIH; www.nih.gov), who was attempting to deal with a high incidence of jaundice among servicemen inoculated with the yellow fever vaccine before being sent to the South Pacific. Dyer arranged for Kornberg's transfer from sea duty to research at the NIH. The die was cast. Kornberg was never to return to clinical medicine, and the course of his research career was set. Largely because of Joseph Goldberger's influence, the focus at the NIH at the time was on the role of vitamins in nutrition. Goldberger, one of the greatest of the 'vitamin hunters' had, in the 1920s, recognized that the disease pellagra was caused not by a microbe, but by a vitamin-B deficiency. Kornberg's initial work was not on jaundice but on the role of bacterial flora in providing adequate amounts of folic acid and vitamin K for rat nutrition [2]. Nutrition research, dominated by the hunt for new vitamins, had occupied a preeminent place in the biochemistry of the 1920s and 1930s. However, by the mid-1940s it was in decline, replaced by the quest for defining the role of the vitamins in intermediary metabolism.

Fascinated by his reading about the work of the great European biochemists: Otto Warburg, Otto Meyerhof, Carl and Gerti Cori, and Severo Ochoa on enzymes, coenzymes and ATP, and influenced by Bernard Horecker, a friend and biochemist at the NIH, Kornberg set about learning the exciting new biochemistry, in particular the search for soluble enzymes that promoted ATP synthesis, then seen to be the most important and exciting problem in biochemistry.

After persuading W.H. Sebrell, his chief at the NIH, for permission to take a leave from his nutrition work,

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Figure 1. Arthur Kornberg (1918–2007). Photo courtesy of Stanford University Visual Arts (www.stanford.edu).

Kornberg joined Severo Ochoa's laboratory at the New York University Medical School (NY, USA) for one year; he later joined Carl and Gerti Cori's laboratory at the Washington University School of Medicine (MO, USA) for an additional six months. During that time, Kornberg purified the malic enzyme from liver and aconitase from muscle [3]. 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. Upon returning 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 Horecker.

Kornberg's first effort in the new Enzymes Section involved the purification of nucleotide pyrophosphatase from potatoes. This humble enzyme, which cleaves the pyrophosphate bond of NAD to yield nicotinamide mononucleotide (NMN) and AMP, exemplified Kornberg's credo 'never a dull enzyme' because it provided him with NMN, which, in turn, led him to the discovery of an enzyme that catalyzes the synthesis of the coenzyme NAD^+ [4] (Eqn 1).

$$NMN + ATP \leftrightarrow NAD^+ + PP_i \qquad \text{[Eqn 1]}$$

Kornberg subsequently showed that another coenzyme, flavin adenine dinucleotide, is synthesized by a similar mechanism, as are nucleotides [5,6]. Over the years, this mechanism of nucleotidyl transfer from a nucleoside triphosphate with the release of inorganic pyrophosphate (PP_i) that Kornberg discovered for coenzyme and nucleotide biosynthesis was found to be a general one for the synthesis phospholipids, peptides and even nucleic acids. The discovery of this release of PP_i was of particular importance because these reactions, with an equilibrium constant near one, can be driven in the direction of synthesis by the presence in all cells of an efficient inorganic pyrophosphatase, which hydrolyzes PP_i to inorganic orthophosphate (P_i).

Discovery of DNA polymerase

Influenced by Carl and Gerti Cori, Kornberg moved to the Washington University School of Medicine to become chairman of the Department of Microbiology. It was there that he assembled a talented young faculty, part of which would subsequently form the core of the Department of Biochemistry at Stanford University (CA, USA). More about that later.

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

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, it was a matter of speculation whether deoxynucleotide precursors were polymerized to form DNA or whether the 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, which he had obtained from Morris Friedkin, a colleague in the Pharmacology Department at Washington University. An extract of *Escherichia coli* was chosen rather than a mammalian tissue such as liver because of its known rapid rate of DNA replication (doubling time of 20 min in rich medium). DNA synthesis was measured by conversion of the acid-soluble thymidine to an acid-insoluble form. The first result was rather unimpressive, ~50 cpm, converted out of ~1 million cpm added. But, importantly, all of the acid-insoluble radioactivity was made acid-soluble by treatment with crystalline pancreatic DNase, which had just then become available. Presumably, the thymidine substrate had been incorporated into DNA.

Again, convinced of the power of enzyme purification in revealing and ultimately reconstituting a pathway of metabolism, Kornberg and his students began to purify the thymidine incorporation activity(s) of the *E. coli* extract. Over a period of approximately two years, with this simple assay to measure DNA synthesis, they discovered (i) the enzyme, which they named DNA polymerase, and (ii) the deoxynucleoside triphosphates (dNTPs), the substrates for the reaction. They further determined that the enzyme did not start a chain *de novo* but, rather, required a DNA 'primer', onto which deoxynucleotides were added. Most importantly, they discovered that a DNA template is required, which serves to guide the DNA polymerase in the selection of the correct dNTP for polymerization according to Chargaff's rules and the Watson–Crick hypothesis [7–9]. Kornberg and his colleagues later demonstrated that, although the enzyme

polymerizes the dNTPs in the 5′→3′ direction, it has a built-in error-correcting mechanism in the form of a 3′→5′ exonuclease, which recognizes insertion of an incorrectly added nucleotide and excises it, enabling the correct nucleotide to be inserted, thereby enhancing the fidelity of replication [10]. Finally, they showed that the reaction mechanism consists of the nucleophilic attack of the α phosphorus of the incoming deoxynucleoside triphosphate on the 3′ hydroxyl group at the primer terminus to form a new phosphodiester bond, thereby extending the primer by a single nucleotide, with the elimination of inorganic pyrophosphate. As in coenzyme and nucleotide synthesis, the reaction is driven in the direction of synthesis by the ubiquitous presence of inorganic pyrophosphatase. This process is repeated sequentially until replication of the DNA template is complete.

The two manuscripts submitted by Kornberg's group in 1958 to the *Journal of Biological Chemistry*, describing the enzymatic synthesis and characterization of the four deoxynucleoside triphosphates, the partial purification of the DNA polymerase, the requirements of the reaction and the characterization of the DNA product, were declined for publication. The criticisms were that DNA synthesis was not proven, that the term 'DNA polymerase' was inappropriate and that the deoxynucleoside triphosphates were not adequately characterized. Through the intervention of John Edsall, who had just been appointed Editor-in-Chief, the decision was reversed and the two papers, in a somewhat modified form, appeared in the July 1958 issue [7,8]. A third paper demonstrating that the polymerase copies a DNA template appeared in the same year in the *Proceedings of the National Academy of Sciences* [9].

For the discovery of the DNA polymerase and the demonstration that DNA synthesis by this enzyme is a template-driven process, Kornberg shared the 1959 Nobel Prize in Physiology or Medicine [11] with Severo Ochoa, who had demonstrated the enzymatic synthesis of polyribonucleotides by reversal of degradative phosphorolysis by polynucleotide phosphorylase.

'Creation of life in the test tube'

After several unsuccessful attempts to demonstrate that the DNA product of DNA polymerase is biologically active, Kornberg and Mehran Goulian in collaboration with Robert Sinsheimer were able to demonstrate the synthesis of infectious circular single-stranded øX174 DNA [12,13]. This achievement, which involved the high-fidelity replication of a 5000-nucleotide viral chromosome, received wide publicity as the 'creation of life in the test tube', was made possible by the discovery, at that time, of the enzyme DNA ligase, which catalyzes the joining of linear DNA molecules and the conversion of linear to circular DNA.

The synthesis of infectious circular øX174 required DNA polymerase, the four deoxynucleoside triphosphates and the DNA ligase from *E. coli*. At the time of the experiment, the co-factor for the *E. coli* DNA ligase, NAD^+, had not yet been identified. However, a boiled extract of *E. coli*, which presumably contained the heat stable, low molecular weight co-factor was used instead. We know now, of course, that DNA polymerase cannot start a chain and requires a primer. Although it first seemed unlikely that such fragments of DNA in the boiled extract would match the øX174 DNA template accurately enough to serve as a primer, it became clear that the DNA polymerase removes the unmatched regions of the fragment by proofreading at the 3′ end by the 3′→5′ exonuclease [10] and at the 5′ end by virtue of the 5′→3′ exonuclease domain of the enzyme [14], which normally serves to remove damaged nucleotides from DNA by excision, followed by re-synthesis of the excised region so that no trace of the fragment remains in the synthetic (and infectious) product. These experiments demonstrated that the DNA polymerase could promote high fidelity and complete chromosomal replication, and generate biologically active molecules.

A multiplicity of DNA polymerases

In the summer of 1969, the role of DNA polymerase in DNA replication came under fire. John Cairns and Paula DeLucia had isolated a mutant of *E. coli* that seemed to lack DNA polymerase activity and yet was fully viable and multiplied at a normal rate. It was, however, abnormally UV sensitive, indicating that the cell was defective in DNA repair. At about the same time, genes were being discovered in *E. coli*, designated as *dna*A, *dna*B, *dna*C and so on, that were essential for normal DNA replication, indicating that DNA polymerase alone could not be responsible for DNA replication; the process must be far more complex than had been thought.

The availability of a mutant of *E. coli* that seemingly lacked DNA polymerase activity triggered a search in extracts of the mutant for another DNA polymerase(s) that would presumably be needed for chromosomal replication, rather than for DNA repair – a seemingly less interesting process to which the DNA polymerase had been relegated and for which, with its active 5′→3′ exonuclease domain, was ideally suited (see earlier). It is ironic that today, DNA repair, with its close connection to cancer, has become an exceedingly active area of investigation, perhaps more so than DNA replication. Within a brief period, several investigators, including Tom Kornberg, Arthur Kornberg's son, discovered not one but two DNA polymerases: DNA polymerase II and DNA polymerase III. These were both clearly distinct from the DNA polymerase discovered by Arthur Kornberg, which was then designated DNA polymerase I. Importantly, DNA polymerase III was shown to be the product of the *dna*E gene and to be absolutely essential for DNA replication.

DNA polymerase III in a complex holoenzyme form is the DNA polymerase that has a central role in DNA replication; however, it is the 5′→3′ exonuclease domain of DNA polymerase I that also possesses RNase H activity, which has an essential role in DNA replication by catalyzing the excision of the RNA primers that initiate synthesis of the discontinuously synthesized Okazaki fragments. In recent years, two more DNA polymerases, DNA polymerase IV and V, have been identified in *E. coli* and, like DNA polymerases I and II, are involved in DNA repair. In eukaryotes, the situation is far more complex. Fifteen distinct DNA polymerases have been identified and the list continues to grow. Three are devoted to the replication

of the genome (DNA polymerases α, δ and ε); DNA polymerase γ replicates the mitochondrial genome; and the rest are all devoted to the repair of specific types of lesion in DNA. There are, in addition, virally encoded DNA polymerases that replicate viral genomes and, in the case of the retroviruses, reverse transcribe the RNA genomes into DNA. Despite their number and diversity, all of these DNA polymerases show the same requirements as those found for DNA polymerase I: a template to guide the polymerase in its base selection, a primer onto which deoxynucleotides are added from the four deoxynucleoside triphosphates and Mg^{2+}. There are factors associated with DNA polymerases, for example, clamps and clamp loaders, and exonucleases that increase the efficiency and fidelity of DNA replication, but the basic mechanisms of replicating a DNA chain are all the same.

Over the years, with the crystallization of many DNA polymerases, the determination of their 3D structures and the application of sophisticated pre-steady state kinetic analysis, their chemical mechanisms are now known in great detail. This information has been particularly valuable in the design of effective chemotherapeutic agents, in particular antiviral drugs.

Replication of a chromosome from start to finish

When it became clear that DNA polymerase I is 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 homogenous single-stranded circular DNA molecules, the genomes of bacteriophages M13 and øX174. With the insight that, unlike DNA polymerase, RNA polymerase does have the capacity to start a chain *de novo* without the need for a primer, Kornberg investigated whether Rifampicin, an RNA polymerase inhibitor, could block 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 the covalent attachment of the deoxyribonucleotides that start the new chain, complementary to the single-stranded M13 chromosome [15]. 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 product of the *E. coli dna*G gene [16]. The RNA primer is subsequently removed by the action of an RNase H either as a distinct enzyme or, as in the case of *E. coli*, the 5′→3′ exonuclease domain of DNA polymerase I [14]. Over a period of approximately ten years, Kornberg and his students identified and assembled a 'replisome' that could convert the single-stranded circular øX174 DNA molecule to its double-stranded 'replicative form'. All of the components of the replisome were products of the *dna*B, *dna*C, *dna*E, etc. genes, known to be essential for *E. coli* chromosomal replication. Particularly noteworthy was the ten-subunit, highly processive DNA polymerase III holoenzyme and the primosome complex with DNA helicase and primase functions, and the single-stranded DNA-binding protein needed to melt the secondary structure in the template [17].

The replisome that Kornberg had assembled consisted of proteins essential for cellular DNA replication and could catalyze the rapid, high-fidelity replication of a single-stranded circular viral genome to yield a double-stranded circular DNA molecule, thereby opening a window to the replication of the *E. coli* genome. However, the question still remained: how is the replication of a duplex DNA molecule initiated, propagated and finally terminated? The solution to this problem came with an understanding of the role of the product of the *dna*A gene, which was not part of the replisome, and the availability of a template consisting of a double-stranded circular DNA molecule into which the *E. coli* origin of replication (OriC) had been inserted. Again using 'the hammer of enzyme purification', supported by the genetics of *E. coli* DNA replication, Kornberg was able, after '12 man years of effort' to finally reconstitute the origin-specific replication of the OriC-containing plasmid, and thereby the replication of the *E. coli* chromosome. As he put it in the title of his lectures on the subject, Kornberg and his students had achieved the 'replication of the *E. coli* chromosome from start to finish' [18]. This monumental achievement has influenced a generation of biochemists to undertake problems seemingly intractable: signal transduction, intracellular protein transport and gene expression, the latter culminating in the elucidation of the 3D structure and the dynamics of mRNA synthesis by the eukaryotic RNA polymerase II complex by his 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 largely 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 analogs turned out to be the key reagent in polymerase chain reaction (PCR) technology and in the sequencing of the human and other genomes.

Bacterial sporulation, membranes and polyphosphate

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 enable a biochemical entré into development [19]. However, the rapid progress in the work on øX174 DNA replication at this time demanded his full attention and the spore project was phased out.

Kornberg's brief entry in the early 1970s into research on cellular membranes followed a sabbatical leave at the Medical Research Council (MRC) Laboratory (Cambridge, UK) and was prompted by the prevailing wisdom that membrane attachment of the *E. coli* chromosome and perhaps the replication machinery is essential for chromosomal replication [20]. 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 in 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 PolyP, a subject that had intrigued him since the 1950s when he and his first wife, Sylvy Kornberg, isolated polyphosphate kinase (PPK) from *E. coli*, an enzyme capable of synthesizing polyphosphate [21]. His studies on PolyP and PPK, which as he put it 'disinterred a molecular fossil', led to the discovery of the role of PolyP in bacterial growth and survival, quorum sensing, biofilm formation, virulence and a wide variety of responses to stress and synthesis. He was convinced that future work would reveal the clinical significance of PolyP and its importance in microbial infections. A review by Michael Brown and Arthur Kornberg on this topic appears in this issue of *TiB*S [22]. Kornberg was actively engaged in the preparation of the article when he died.

Author and scientific leader

Arthur 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* [23], 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 the book, the last of which he co-authored with his graduate student Tania Baker, and his autobiographical *For the Love of Enzymes* [24], 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, a perceptive analysis of the biotech industry* [25]. His last book, *Germ Stories* [26], is a charming collection of poems originally written for his young children and then his grandchildren that 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 Medicine and Physiology, 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 US National Academy of Sciences and the American Academy of Sciences and was a Foreign Member of the British Royal Society. He 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 NIH, in which he spent his formative years as a biochemist and which he regarded as his true *alma mater* [27,28].

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 (MA, USA). 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 myself, and Robert Baldwin from the University of Wisconsin–Madison (WI, USA).

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 achieved national and international renown.

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 post-doctoral 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 the sharing of crucial reagents and new methods. This practice greatly facilitated the development of recombinant-DNA technology at Stanford. Such an arrangement, which regrettably does not seem to have been adopted often elsewhere, obviously requires small research groups 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 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, winner of the 2006 Nobel Prize in Chemistry, Thomas Kornberg, Professor and Vice-Chairman of Biochemistry and Biophysics at the University of California (SF, USA), 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. New and unexpected findings were being made almost every day and all of us in our small group, consisting – in addition to Arthur – of myself and Maurice Bessman, Postdoctoral Fellows, Ernie Simms, Arthur's research assistant and his wife Sylvy Kornberg, shared in the joy and excitement of these discoveries.

Arthur's research style, 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.

References

1 Kornberg, A. (1942) Latent liver disease in persons recovered from catarrhal jaundice and in otherwise normal medical students as revealed by the bilirubin excretion test. *J. Clin. Invest.* 21, 299–308

2 Kornberg, A. *et al.* (1944) The effect of *L. casei* factor ('Folic Acid') on blood regeneration following hemorrhage in rats. *Am. J. Physiol.* 142, 604–614
3 Kornberg, A. *et al.* (1948) Spectrophotometric studies on the decarboxylation of β-keto acids. *J. Biol. Chem.* 174, 159–172
4 Kornberg, A. (1950) Reversible enzymatic synthesis of diphosphopyridine nucleotide and inorganic pyrophosphate. *J. Biol. Chem.* 182, 779–793
5 Schrecker, A.W. and Kornberg, A. (1950) Reversible enzymatic synthesis of flavin-adenine dinucleotide. *J. Biol. Chem.* 182, 795–803
6 Kornberg, A. *et al.* (1954) Enzymatic synthesis of pyrimidine and purine nucleotides. I. Formation of 5-phosphoribosylpyrophosphate. *J. Am. Chem. Soc.* 76, 2027–2028
7 Lehman, I.R. *et al.* (1958) Enzymatic synthesis of deoxyribonucleic acid. I. Preparation of substrates and partial purification of an enzyme from *Escherichia coli*. *J. Biol. Chem.* 233, 163–170
8 Bessman, M.J. *et al.* (1958) Enzymatic synthesis of deoxyribonucleic acid. II. General properties of the reaction. *J. Biol. Chem.* 233, 171–177
9 Lehman, I.R. *et al.* (1958) Enzymatic synthesis of deoxyribonucleic acid. V. Chemical composition of enzymatically synthesized deoxyribonucleic acid. *Proc. Natl. Acad. Sci. U. S. A.* 44, 1191–1196
10 Brutlag, D. and Kornberg, A. (1972) Enzymatic synthesis of deoxyribonucleic acid. XXXVI. A proofreading function for the 3′→5′ exonuclease activity in deoxyribonucleic acid polymerase. *J. Biol. Chem.* 247, 241–248
11 Kornberg, A. (1960) Biologic synthesis of deoxyribonucleic acid. *Science* 131, 1503–1508
12 Goulian, M. and Kornberg, A. (1967) Enzymatic synthesis of DNA. XXIII. Synthesis of circular replicative form of phage øX174 DNA. *Proc. Natl. Acad. Sci. U. S. A.* 58, 1723–1730
13 Goulian, M. *et al.* (1967) Enzymatic synthesis of DNA. XXIV. Synthesis of infectious phage øX174. *Proc. Natl. Acad. Sci. U. S. A.* 58, 2321–2328
14 Setlow, P. and Kornberg, A. (1972) Deoxyribonucleic acid polymerase: two distinct enzymes in one polypeptide. II. A proteolytic fragment containing the 5′→3′ exonuclease function. Restoration of intact enzyme functions from two proteolytic fragments. *J. Biol. Chem.* 247, 232–240
15 Brutlag, D. *et al.* (1971) A possible role for RNA polymerase in the initiation of M13 DNA synthesis. *Proc. Natl. Acad. Sci. U. S. A.* 68, 2826–2829
16 Schekman, R. *et al.* (1972) Initiation of DNA synthesis: synthesis of øX174 replicative form requires RNA synthesis resistant to rifampicin. *Proc. Natl. Acad. Sci. U. S. A.* 69, 2691–2695
17 Schekman, R. *et al.* (1974) Multienzyme systems of DNA replication. *Science* 186, 987–993
18 Fuller, R.S. *et al.* (1981) Enzymatic replication of the origin of the *Escherichia coli* chromosome. *Proc. Natl. Acad. Sci. U. S. A.* 78, 7370–7374
19 Kornberg, A. *et al.* (1968) Origin of proteins in sporulation. *Annu. Rev. Biochem.* 37, 51–78
20 Crooke, E. *et al.* (1992) The chromosome origin of *Escherichia coli* stabilizes DnaA protein during rejuvenation by phospholipids. *J. Biol. Chem.* 267, 16779–16782
21 Kornberg, A. *et al.* (1956) Metaphosphate synthesis by an enzyme from *Escherichia coli*. *Biochim. Biophys. Acta* 20, 215–227
22 Brown, M.R.W. and Kornberg, A. The long and short of it – polyphosphate, PPK and bacterial survival. *Trends Biochem. Sci.* DOI:10.1016/j.tibs.2008.04.005 (this issue)
23 Kornberg, A. and Baker, T.A. (1992) *DNA Replication* (2nd edn), W.H. Freeman
24 Kornberg, A. (1989) *For the Love of Enzymes: Odyssey of a Biochemist,* Harvard University Press
25 Kornberg, A. (1995) *The Golden Helix: Inside Biotech Ventures,* University Science Books
26 Kornberg, A. (2007) *Germ Stories,* University Science Books
27 Kornberg, A. (1992) Basic research: the lifeline of medicine. *FASEB J.* 6, 3143–3145
28 Kornberg, A. (1997) The NIH did it. *Science* 278, 1863