A Life in Biochemistry

For the Love of Enzymes. The Odyssey of a Biochemist. ARTHUR KORNBERG. Harvard University Press, Cambridge, MA, 1989. xvi, 336 pp., illus. $29.95.

Biochemistry in the United States prior to the 1930s was largely occupied with problems of analysis. Dynamic biochemistry, aiming at nothing less than an understanding in molecular terms of the whole pattern of processes occurring in living cells, was imported into the United States by a wave of biochemists driven from Europe by the Nazis. After World War II, the United States was to become, temporarily at least, the world center of biochemistry, thanks to the enlightened policies of the National Institutes of Health. A veritable army of able U.S. biochemists emerged. The really towering figures in the history of biochemistry, however, still reflect its European origins. F. G. Hopkins, Otto Warburg, Carl Cori, and Fritz Lipmann come to mind as those who shaped modern biochemistry not only by their experiments but also by the force of their personalities and their influence on future directions of research. The one native American who might by general assent be admitted to that select company is Arthur Kornberg, professor of biochemistry at Stanford University.

Kornberg's new book *For the Love of Enzymes: The Odyssey of a Biochemist* traces the origins and development of his research on the biosynthesis of DNA, work that was to bring him a Nobel Prize in 1959. Although largely devoted to science, the book is written from a distinctly personal point of view, which adds greatly to its interest not only because of what we learn about Kornberg the man but also because of the light it sheds on how the personality of a researcher may be reflected in the style of his work.

Born in New York City of Jewish immigrant parents, Kornberg was reared in a family atmosphere now recognized as archetypical of that background and period. He proved to be a gifted student. Rather than attend nearby Brooklyn College, he chose to spend three hours a day commuting via subway to the City College of New York, then in its days of glory, a magnet for many other brilliant Jewish students who could not afford to attend Ivy League universities and who probably would not have been admitted if they could. He became one of 200 premedical students who were graduated from City College in 1937. The virulence of the anti-Semitism of that day was such that only five of them were offered admission to medical school. Kornberg became one of the quota of two Jews to enter the University of Rochester Medical School, there to encounter a pattern of prejudice and unfairness that still provokes his bitterness and anger almost 50 years later.

A newly fledged M.D. in 1942, Kornberg served briefly in the Navy as a ship's physician before being appointed to a research position at NIH. There he worked on problems of nutrition but became increasingly aware that the period of great excitement in that area was drawing to a close. At the end of World War II, he turned to the rapidly developing field of enzymology, working as a postdoctoral fellow in the laboratories first of Severo Ochoa (with whom he was later to share the Nobel Prize) and then of Carl Cori at Washington University. He returned to a newly organized enzyme section at NIH.

In 1953, Kornberg left NIH to move to Washington University Medical School as chairman of the department of microbiology. He was apparently never altogether comfortable in that role, and in 1959 he and virtually his entire department moved to form a new department of biochemistry at Stanford. The development and leadership of this superb department during his ten years as chairman are not the least of Kornberg's accomplishments.

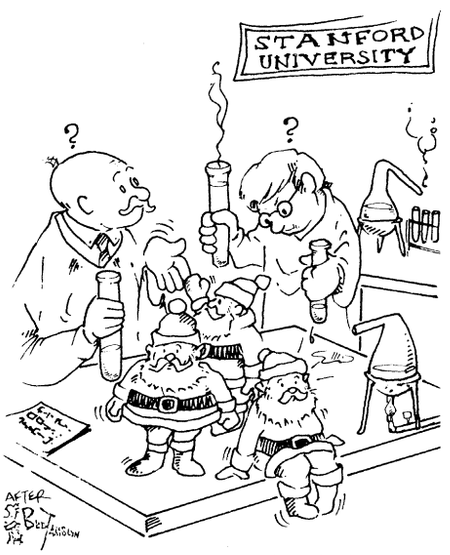
The problem of DNA replication is one of the great pinnacles of modern biology, but Kornberg's approach to it was characteristically step by step. While still at NIH, he purified an enzyme that split the coenzyme nicotinamide adenine dinucleotide (NAD) at the pyrophosphate bond. His success confirmed his belief in the power of enzyme purification as a tool in biological research, a doctrine of which he was to become the passionate advocate. (He tells us, however, that the dictum "Don't waste clean thoughts on dirty enzymes," almost universally attributed to him, should really be credited to Efraim Racker.) One of the products of the reaction catalyzed by the potato enzyme is nicotinamide ribose phosphate (NRP). The availability of NRP led him to study the *synthesis* of NAD, which he found to occur by the following reaction:

$$\text{Nic-ribose–P} + \text{P–P*–P–Ad} \rightleftharpoons \text{Nic-ribose–P–P–Ad} + \text{P–P*}$$

This discovery was an eye-opener. The elimination of inorganic pyrophosphate (P–P) from a nucleoside triphosphate (such as ATP) first observed here proved to be a very general feature of biosynthetic reactions. Because NAD synthesis also involves the transfer of an activated nucleotide building block, it also offered insight into the much more challenging problem of the biosynthesis of DNA and RNA, then looming only distantly.

In 1955, while still at Washington University, and greatly aided by a gift of radioactive thymine (one of the bases in DNA) from Morris Friedkin, Kornberg carried out the experiment that is now part of the folklore of enzymology. A trace amount (68 disintegrations per minute) of radioactivity was converted in the test tube, in a reaction catalyzed by a cell-free extract of *Escherichia coli*, to an acid-insoluble product that might (or might not) represent DNA. This was the opening wedge, driven (to use Kornberg's metaphor) by the hammer of enzyme purification, that opened the way to the eventual isolation of DNA polymerase I. This enzyme uses DNA as a template to form a complementary chain of DNA from a mixture of the four deoxyribonucleoside triphosphates. As each nucleotide is added to the growing polymer, inorganic pyrophosphate is eliminated. Little wonder that it was said of Kornberg that everything he touched turned to pyrophosphate.

The discovery of polymerase I was pivotal, because it proved to be the prototype of all other DNA polymerases. The later dis-



"I don't understand it either!"

Newspaper cartoon, 15 December 1967, following production of synthetic viral DNA in Arthur Kornberg's laboratory at Stanford. "After twelve years of trying, we had finally done it—we had gotten DNA polymerase to assemble a DNA chain with the identical form, composition, sequence, and genetic activity of DNA from a natural virus . . . . Despite our disclaimers, there was still enough excitement left . . . about creating 'life' in the test tube to make front page stories in virtually all newspapers worldwide." [From *For the Love of Enzymes*]

covery by John Cairns of a mutant strain of *E. coli* that apparently lacked DNA polymerase I seemed to indicate that it is not an essential enzyme. Kornberg reveals that he had bet his colleague Buzz Baldwin a bottle of champagne that the nuclease (DNA-destroying) activities found in preparations of DNA polymerase I are not intrinsic properties of that enzyme. Later he was forced to pay up on this bet. Furthermore, according to present views, polymerase I *is* an essential enzyme, and it is probably its nuclease activity that makes it so.

The controversy about polymerase I spurred the search that led to the discovery of polymerase III, a multicomponent enzyme complex that is the principal catalyst of DNA synthesis during the replication of the *E. coli* chromosome. The ice jam broke, and a flood of discoveries in laboratories all over the world greatly enlarged our knowledge of DNA replication. Kornberg summarizes these new advances in masterly fashion.

The book also conveys a strong sense of Kornberg's scientific style and the vigor of his personality and opinions. His appetite for work is phenomenal, and his determination never to waste time, the irreplaceable commodity, is almost an obsession. During his stay at NIH, he and his colleagues Herbert Tabor, Leon Heppel, and Bernard Horecker, all of whom were to emerge as leaders in their own fields, set up a seminar that met at noon every day so that the time required for lunch would not be wasted. According to legend, when the Budapest Quartet was playing at the Library of Congress the demand for tickets made it necessary to appear at the box office at 6 o'clock in the morning. On those days the seminar was held with the participants standing in line.

Kornberg himself tells us that on one occasion his laboratory assistant Bill Pricer lost a sample through a mishap in the centrifuge. He assured Kornberg that nothing had been lost—there was another sample available. Kornberg's reply was: "The hour lost can never be recovered."

The impression that one may thus gain of an austere and rather daunting figure is counterbalanced by the picture that also emerges from the book of man who has won the affection as well as the admiration of his colleagues and whose dedication to his family is deep. Indeed, Kornberg's family life became interwoven with his work to a degree unusual for a researcher. His first wife, Sylvy, was a distinguished biochemist in her own right, as are his sons Roger and Tom. A third son, Ken, is an architect, one of whose specialities, fittingly enough, is the design of laboratories. Kornberg's second wife, Charlene, is an artist who provided illustrations for this book.

The fusion of biochemistry and genetics that has led to the dramatic emergence of molecular biology and genetic engineering in the past few decades is perhaps the most notable event in science in the later 20th century. *For the Love of Enzymes* offers a unique and fascinating insight into the life and thought of a man whose work was at the center of these grand developments.

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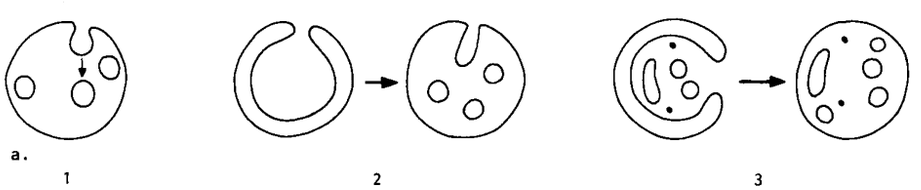
Organelles Observed

Lysosomes. ERIC HOLTZMAN. Plenum, New York, 1989. xiv, 439 pp., illus. $59.50. Cellular Organelles.

The idea that eukaryotic cells contain acidic digestive organelles—analogous to "intracellular stomachs"—dates back to before the turn of the century, to the early observations of Elie Metchnikoff. Though lysosomes thus have a long and rich history, their entry into the "classical era" of cell biology did not occur until much later; if this was marked by any single event, it was the convening of a Ciba Foundation symposium on lysosomes in London in 1963. As a result of the combined efforts of de Duve, Novikoff, Straus, and others, it was then clearly established that lysosomes were discrete entities that were of heavy density, rich in hydrolytic enzymes with acidic *p*H optima, and active in the degradation of endogenous material as well as exogenous material internalized by endocytosis. Alterations in lysosome function associated with various pathological states were also beginning to be appreciated, although lysosomal storage diseases were yet unknown. During the last decade, the virtual explosion of information concerning lysosomes has moved study of these organelles solidly into the "modern era" of molecular cell biology. We have now begun to understand many aspects of lysosome structure, function, genetics, pathology, and biogenesis at the molecular level. A great deal is known and a great deal is being learned, and rapidly.

Eric Holtzman's *Lysosomes* is described as an "advanced text" and bravely attempts to span both historical perspective and current research in this rapidly advancing area. The title of the book, which is actually Holtzman's second monograph on the topic (the first was published in 1976, near the end of the above-mentioned classical era), is somewhat misleading, since a variety of other related topics are considered, including endocytosis, cell surface receptors, and endocytic organelles in diverse cell types (including plants, yeast, and protozooans). This reflects the fact that lysosomes are as interesting for the material targeted to them by endocytosis, biosynthesis, or autophagy as for their own intrinsic properties. The book is remarkably up to date (as of early 1988) and touches on virtually every major issue facing the field today. It is a lovingly written compendium by a literate and articulate scientist who has been a lysosome watcher for many years.



"Formation of multivesicular bodies. (**a**) The vesicles within heterophagic multivesicular bodies ('multivesicular endosomes') can arise by invagination of the membrane bounding an endosome: vesicles can bud off directly as in **1** or larger, cuplike invaginations can form and subsequently fragment into vesicles (**2**). **3** illustrates an alternative mode of formation of a multivesicular-type structure, through the autophagic-like engulfment of pre-existing vesicles. **b** is from a neuron in a mouse ganglion and shows a cuplike structure (arrow), apparently generating its internal vesicles;" ×~55,000. [From *Lysosomes*]