Book Reviews

The Origins of Modern Biochemistry

Biological Phosphorylations. Development of Concepts. HERMAN M. KALCKAR. Prentice-Hall, Englewood Cliffs, N.J., 1969. xx + 740 pp., illus. $14.95. Prentice-Hall Biological Science Series.

For those who wish to see in perspective some of the great achievements of modern biochemistry, this book is unique. There are already some excellent collections of important papers on bacterial genetics and bacterial viruses, edited with valuable introductions by E. A. Adelberg and Gunther Stent, respectively. The volume in honor of Max Delbrück, *Phage and the Origins of Molecular Biology*, has recorded many personal recollections by participants in the pioneering studies on bacteriophage, and J. D. Watson in *The Double Helix* has set down the story of the DNA structure from his personal point of view. Yet there has been no comparable attempt to portray the origins of modern biochemistry—a field as fundamental as molecular genetics, with which it is now inextricably intertwined. In 1935, indeed, Fritz Lieben published a useful *Geschichte der Physiologischen Chemie*, which in its time was fairly comprehensive, though not especially profound or original in its insights. David Keilin's posthumously published *History of Cell Respiration and Cytochrome* (1966) is the most notable contribution to the history of biochemistry in recent years.

Kalckar's book differs from any of these, not only in subject matter but in approach. To those who are not familiar with modern biochemistry, the title *Biological Phosphorylations* might suggest a rather narrow field. In fact it encompasses a large and central portion of biochemistry. It is primarily through phosphorylation and its reversal that the living cell stores and releases energy. Fermentation, oxidation, the activities of mitochondria, the transformation of chemical into mechanical energy in muscle and other contractile tissues—all these are part of the story of phosphorylation, and this book traces the development of them all. The story is told in the words of the original discoverers, by the reprinting of some of their crucial papers, in whole or in part. For each of the ten sections into which he has grouped the papers Kalckar also writes a thoughtful and highly personal introduction. He has himself been a major contributor to several of the developments that unfold as the book proceeds and he has known well many of the other principal actors in the drama; and all this endows his comments with special significance.

The first paper reprinted here is that of Harden and Young (1905) which revealed the significance of phosphate for alcoholic fermentation and demonstrated the presence of an essential coenzyme. Then we jump 20 years to take up the development of knowledge of the glycolytic cycle, as told by its discoverers, Otto Meyerhof, Gustav Embden, and their successors. Notable is the work of C. H. Fiske and Y. Subbarow, who in the course of some three years (1926–1929) identified and purified two key compounds, phosphocreatine and adenosine triphosphate (ATP), the latter being independently obtained in Meyerhof's laboratory by K. Lohmann, whose work is also represented here. The following section deals with oxidative phosphorylation, in which the energy supplied by the reduction of oxygen is converted into the "phosphate bond energy" of ATP, the chief energy source for driving other processes in the living cell. In this field Kalckar was himself one of the major pioneers. Here we have available, in translation from the Russian, the crucially important paper of V. A. Belitser and E. T. Tsybakova (1939)—which probably few American biochemists have actually read—and a series of later developments taking us up to the work of D. I. Arnon (1965) and A. T. Jagendorf (1966) on photosynthetic phosphorylation. In spite of intensive studies by a group of brilliant investigators, however, this field of study remains baffling in many respects.

Most of the remaining sections of the book (parts 3 through 7) revolve around the problem of muscular contraction, its chemistry and energetics. Kalckar starts here with the work of W. M. Fletcher and F. G. Hopkins (1907) on the formation and disappearance of lactic acid in muscle, which marked the beginning of the modern era in the biochemistry of muscle. The subsequent developments furnish a beautiful example of the progress and the pitfalls of research. The great work of Meyerhof and of A. V. Hill (1920–30) focused almost entirely on the conversion of glycogen to lactic acid as the basis of muscular contraction. The simplicity of the picture they evolved was shattered in 1929 by Einar Lundsgaard's discovery that muscular contraction, in muscles treated with iodoacetate, can proceed with no lactic acid formation at all, the energy being supplied by the breakdown of the phosphate bonds in phosphocreatine and ATP. Lundsgaard's masterly analysis of the situation, here presented in a paper previously available only in Danish, is outstanding. His work opened up new vistas, and led within a few years to a detailed picture of the chemical events in muscle in the absence of oxygen, largely worked out in the laboratories of Meyerhof, Embden, and Otto Warburg. Hill continued to refine his measurements on heat production and mechanical work in muscle; his "challenge to biochemists" (1950) to prove some of the statements they made without adequate evidence has been a powerful stimulus to much recent work.

The story is instructive in many ways. It shows how even the most gifted scientists can take an incomplete picture for the whole story. This brilliant work of Meyerhof and Hill was thoroughly sound and has stood the test of time; but the key events, most intimately related to the contractile process, were not even suspected for several years after Meyerhof and Hill received the Nobel Prize in 1922. Also, as progress continued, the investigation of the glycolytic cycle in muscle revealed its intimate relation to alcoholic fermentation in yeast; the complex patterns of both sets of events, superficially so different, proved to be identical in most respects—a most striking example of the fundamental unity of life processes on the biochemical level. One may note another point, not explicitly stressed in the book. The record shows that, from 1920 to 1933, Germany was the great center of research in this field, as in so many others, with England a close second. The decline of science under the Nazis, and its subsequent growth in the United States—much of it catalyzed by refugees from Nazi Germany—shows how rapidly a great country can lose scientific leadership, along with other even more precious things, when taken over by a political regime that is hostile to all disinterested inquiry.

The discovery in 1939, by W. A. Engelhardt and M. N. Ljubimova, that myosin, the chief structural protein of muscle, is also a catalyst for the hydrolysis of ATP indicated for the first time how the structural elements of the muscle fiber appear to be coupled with the mechanism of energy release. Engelhardt's survey of the field (1942), beginning on page 444 of this volume, shows his farsighted vision of things to come. The later developments concerning muscle that the book presents are too numerous to permit even mention of the names of their authors, great as many of them are. I make an exception for the epoch-making work of H. E. Huxley on the double array of filaments in striated muscle, and his sliding filament theory of contraction. It is regrettable that the reprinting (pp. 552–79) does not do justice to the superb quality of the electron micrographs in the original paper and that the captions for the figures were omitted (a printed slip containing these has been provided by the publishers in later copies of the book).

One major aspect of muscle biochemistry is not included—namely, the role of calcium ions in activating the contractile process, and their removal by the sarcoplasmic reticulum during relaxation. Here too ATP plays its part, and it would be good to have something about this in a future edition.

Part 8 of the book, on precursors of polymers, presents some of the papers that were turning points in our knowledge of the biosynthesis of glycogen, nucleic acids, and proteins. Its length is modest—45 pages, compared to some 300 devoted to muscle. This section could easily be expanded into a large book all by itself, but it is good to have these crucial papers brought together, with Kalckar's thoughtful remarks to introduce them. Part 9 deals with the regulation of energy metabolism, and the introductory section here is particularly interesting. Part 10, on organic chemistry and "bioengineering," consists of a single page of text by Kalckar, with nine references; this could be expanded to advantage in a later edition. There is a thoughtful, philosophical three-page epilogue.

A large number of photographs of those who were involved in the story told here enliven the book; although I happen to be among those included, I believe I can be objective in saying that this adds to the value of the book.

All the papers are in English: Kalckar himself has translated most of those that originally appeared in foreign languages, except for those in Russian, where others have helped. In many cases only the most crucial sections of the original papers are given here, as for instance with Fritz Lipmann's epoch-making review of 1941 on phosphate bond energy. In numerous cases a short preliminary note is reprinted here, rather than the later extensive paper—see, for instance, Fiske and Subbarow on phosphocreatine or Ochoa on oxidative phosphorylation. It would be helpful in such cases to give the reader the reference where the full report can be found and to indicate explicitly in longer papers the points at which sections have been omitted. It would also be very helpful to provide cross references between some of the papers reprinted here; for instance, between the work of Fiske and Subbarow (p. 34) and that of Eggleton and Eggleton (p. 340). The most serious deficiency in the book is the lack of an index; this should certainly be remedied in another printing.

One may hope that other books like this will be forthcoming, to deal with other major aspects of biochemistry; and, furthermore, that efforts will be made, through the preservation and study of letters, unpublished documents, and personal recollections, to supplement and enrich the record of the already published literature. In any case Kalckar's book deserves the warmest welcome from all who care to learn how biochemistry came to be what it is today.

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Modes of Explanation and the Tension of Biology

Towards a Theoretical Biology. Vol. 2. Sketches. An International Union of Biological Sciences Symposium, Aug. 1967. C. H. WADDINGTON, Ed. Aldine, Chicago, 1969. viii + 532 pp., illus. $12.50.

This symposium will thoroughly irritate any biologist who comes across it. At first sight it contains a lot of talk and precious little deductive theory; a closer look reveals essays violently attacking the accepted modes of scientific explanation and espousing a biology reformed along more Aristotelian lines. Worse yet, these essays were written by reputable physicists still practicing their trade, emphatically not the "carpenters blaming their tools" who frequent so many theoretical biology congresses. What happened?

This symposium records the attempts of some very intelligent people to digest and understand the disturbing complexities of biology. Many have read Kuhn on scientific revolution, and realize that current models of scientific explanation are as temporary as their predecessors: they are willing to face the possibility that a general theory like that embodied in Einstein's laws and Maxwell's equations is impossible in biology. How do they respond?

Some speakers settle for autonomous theories covering limited aspects of biology: they provide the symposium's only examples of meaningful mathematics. Maynard Smith discusses population genetics, analyzing the preconditions for natural selection and showing how differential reproduction inevitably alters the genetical composition of a population. Kerner and Goodwin apply the techniques of statistical mechanics to interpret otherwise insoluble equations describing, in Kerner's case, the population fluctuations of different species in a community and, in Goodwin's, oscillations in concentration of different enzymes and messenger RNA's. Statistical mechanics is an appealing subject (indeed, one speaker devoted a whole talk to describing just how appealing it is): it can derive a macroscopic from a microscopic level of generalization and works even if we know little about the microscopic interactions. Moreover, one need not determine initial positions and velocities of all the molecules of a gas to apply these techniques, for a gas of given energy and volume would exhibit the same *statistical* behavior for nearly any set of initial conditions. Kerner's treatment holds great promise for ecol-