The Evolution of Biochemistry

Molecules and Life. Historical Essays on the Interplay of Chemistry and Biology. JOSEPH S. FRUTON. Wiley-Interscience, New York, 1972. xii, 580 pp., illus. $19.95.

A History of Biochemistry. Part 1, Proto-Biochemistry; Part 2, From Proto-Biochemistry to Biochemistry. MARCEL FLORKIN. Elsevier, New York, 1972. xviii, 344 pp., illus. $27.75. Comprehensive Biochemistry, vol. 30.

Biochemistry is one of the great areas of scientific advance in our time, but its history has until recently been largely neglected. Until very recently, only one book, Fritz Lieben's *Geschichte der physiologischen Chemie* (Leipzig and Vienna, 1935; reprinted by Georg Olms Verlag, Hildesheim, 1970) stood out as a major contribution. Lieben's emphasis was more on the chemical than on the biological side of the subject, and his story, of course, ended shortly after 1930, when the greatest events were still to come; but within these limits his book is still an indispensable source for anyone seriously concerned with the development of biochemistry.

Recently, significant historical studies have begun again. David Keilin's *History of Cell Respiration and Cytochrome* (Cambridge University Press, 1966) was a major contribution on one great field of biochemistry, and Dorothy Needham's *Machina Carnis* (Cambridge University Press, 1971; reviewed in *Science* **177**, 877 [1972]) treated the history of the physiology and biochemistry of muscular contraction in extraordinary breadth and depth. There have been other contributions, such as the essays in *The Chemistry of Life* (Joseph Needham, Ed.; Cambridge University Press, 1970); and a number of important articles by Mikuláš Teich, who is almost unique among professional historians of science today in devoting his attention particularly to biochemistry. In the borderline area between genetics and biochemistry is Gunther Stent's *Molecular Genetics* (Freeman, 1971), which provides much historical perspective in that great area.

The new books by Fruton and by Florkin, on which I report here, treat the history of biochemistry in greater breadth and depth than any writer since Lieben. The two books differ in aim and scope.

Florkin clearly aims at a comprehensive history of biochemistry, from Greek antiquity to the present. It will ultimately be complete in four volumes, of which this is the first. As yet, therefore, one cannot judge the work as a whole. However, the appearance of the first volume, to which I return later, is a significant event.

Fruton's book is complete as it stands. He limits himself to events occurring in the period about 1800–1950. beginning with Lavoisier and ending at the time of discovery of the double helix structure of DNA. He does not attempt to cover the whole field of biochemistry, but concentrates on five major themes—ferments and enzymes; the nature of proteins; nucleic acids, from Miescher to Watson and Crick; intracellular respiration; and pathways of biochemical change. These topics are not the whole of biochemistry, but they do include the greatest and most central themes. The emphasis is on the interplay of experiments and concepts, as they can be followed in the published literature. Fruton naturally deals with the work of many famous men, as well as others less known, but he explicitly renounces the attempt to provide "potted biographies" of these workers. The emphasis is on the work, not on the personal histories of the investigators. There is a valuable introduction, of 21 pages, where Fruton considers the growth of biochemistry, and the social and institutional framework of that growth, in Europe and America. Thereafter the focus is quite strictly on the concepts and experiments. The style is sober and restrained; Fruton does not attempt to dramatize the sometimes passionate controversies in which some of the major scientists were involved. He clearly wants to emphasize the slow and difficult process of building the solid chemical foundations that made possible the great advances of more recent years, and to counteract the tendency to see the progress of science in terms of a few dramatic "breakthroughs."

After the introduction, the first chapter retells the story of ferments and enzymes, the controversies over the nature of fermentation, and the emergence of the modern concepts of enzymes after the work of Buchner on alcoholic fermentation. Much of this story has been told often before, but Fruton brings new and valuable insights to it. The next chapter, on the nature of proteins, though it owes much to the earlier historical studies of H. B. Vickery, provides a general perspective on the subject which I believe cannot be matched elsewhere. It conveys well the immense difficulties encountered by the earlier investigators in working with substances so complex, so unstable, and so intractable to the techniques available to the chemists of the 19th and early 20th centuries. It was more than 80 years from the first isolation of amino acids from protein hydrolyzates to the formulation of the peptide linkage hypothesis of protein structure, by Franz Hofmeister, and Emil Fischer, in 1902. From then on, the peptide hypothesis dominated the field, although it was subjected to recurrent attacks at intervals over the next 40 years. It was more than a generation after Hofmeister and Fischer before the list of amino acids commonly found in proteins was complete, and a decade after that before a quantitative balance sheet for the amino acid composition of any single protein was available. The really dramatic change has come over the last quarter century, for we can now write complete structural formulas for hundreds of proteins, and three-dimensional structures at high resolution are available for a few dozen. This represents a transformation that is still almost incredible to protein chemists of the older generation, like myself. Fruton's account takes us from the very early years of the 19th century, through the long era of confusion and controversy, to the crucial period of transition from about 1945 on, that has led to the modern age of protein chemistry.

The following chapter, "From nuclein to the double helix," gives the best account I know of the discovery of DNA by Friedrich Miescher, just over a century ago, the development of work on the nucleic acids, and the shifting views of chemists and biologists concerning their possible role in heredity. Certainly by 1885 the definite idea had been expressed that "nuclein," probably meaning nucleoprotein rather than nucleic acid, provided the physical basis of inheritance; and E. B. Wilson, in the first edition of his great treatise *The Cell* (1896), supported this view. Then the chemical studies of P. A. Levene on nucleic acids, while yielding structural information of great importance, also led Levene to suggest that nucleic acids were built on a simple pattern of repeating tetranucleotides. It was obvious that, if this was indeed the pattern of nucleic acid structure, then nucleic acids could not possibly contain the complex variety of information that must be carried by the gene. Thus Wilson, in the third edition of his book (1925), abandoned his earlier emphasis on nuclein, and assigned the major role to the proteins as carriers of heredity. This view held uneasy sway for about 20 years, but the work of Avery on DNA as the transforming factor in pneumococci, and soon after the analytical studies of Chargaff, which rendered the tetranucleotide hypothesis untenable, changed the whole outlook again. (There is evidence that Levene took that hypothesis less seriously than some of his followers.) The later developments, which Fruton also describes well, are too well known to need further comment here. No brief summary can do justice to the many complex, interrelated developments that unfold in this chapter; it should be required reading for those who want to know the chemical background of modern biochemical genetics.

The next chapter, on intracellular respiration, traces the history of this subject from Lavoisier through the gradual unraveling of the complexities of glycolysis and the Krebs tricarboxylic cycle, the work of Otto Warburg, Keilin, and others, on the chain of enzymes involved in biological oxidations and reductions, and the early studies on oxidative phosphorylation. The last chapter, on pathways of biochemical change, traces the growth of knowledge of intermediary metabolism. The crucial period of transition here came in the mid-1930's when Rudolf Schoenheimer and David Rittenberg introduced isotopic labels into fats and proteins and demonstrated the incessant interchanges that occur between the materials supplied in the diet and the constituents of the tissues, and between one tissue and another. This rapidly swept away the previous concepts of separate "exogenous" and "endogenous" metabolism, which had dominated the thinking of biochemists for a generation after Otto Folin had formulated them in 1905. Those of us who lived through the period of Schoenheimer's work will never forget how he opened new horizons in the study of living organisms by his decisive evidence for the "dynamic state" of body constituents. Subsequent developments in this field have been so numerous and so rapid that they have eclipsed all this earlier work in the minds of most younger biochemists. Many of them today, I suspect, hardly know who Schoenheimer was; yet his work represents the beginning of a new era in the study of metabolism.

Fruton concludes his book with a final section on the integration of biochemical processes in the living organism, and the relation of the whole to its parts. The book as a whole is a remarkable achievement, and a landmark in its field.

Florkin's first volume deals, in its first 100 pages, with protobiochemistry, a term introduced by Joseph Needham to cover the developments in the many centuries preceding the foundation of modern chemistry by Lavoisier and Dalton. The work and thoughts of the Greeks receive considerable attention; thence, Florkin passes to alchemy and iatrochemistry, touching very briefly on developments in China and the Arab world, and dealing more extensively with the late medieval alchemists, the iatrochemists, and the phlogistonists. The early work on respiration and animal heat, and the discovery of photosynthesis, come in this period.

The rest of this volume (some 200 pages) deals with the metabolic theories of Lavoisier and his followers, alcoholic fermentation, the rise of the cell theory, the rise and fall of Liebig's metabolic theories, the gradual recognition of the intracellular location of metabolic change, the conflicts between "chemicalists" and vitalists, the rise of physiological chemistry from about 1840 on, and the emergence of biochemistry as a distinctive field in the early 20th century. Florkin traces concepts of "dynamic permanence" of the constituents of the living organism, from the time of Schwann and Claude Bernard to Schoenheimer's concept of the dynamic state of body constituents; the transition from the 19th century to Schoenheimer seems unduly abrupt. Florkin deals with energy metabolism and bioenergetics, from early days to the discovery of oxidative phosphorylation; with biocatalysis and the controversy over the nature of enzymes, and its resolution by the work of Sumner and Northrop; and with the evolution of the knowledge of proteins as well-defined molecules. The final chapter deals with the biochemistry of the cell, with special emphasis on the work of Albert Claude and C. de Duve. The book is enlivened with a large collection of well-reproduced full-page portraits and photographs of notable investigators. Future volumes are to deal with the identification of the sources of free energy in organisms, the unraveling of biosynthetic pathways, the history of molecular interpretations of the biological concepts, and the conception of life as the expression of molecular order.

On a number of topics, Florkin's first volume overlaps with Fruton's treatment. Florkin deals more fully than Fruton with the work of some important investigators, such as Chevreul and especially Theodor Schwann, about whom he has previously written a book. He treats in considerable detail the work on energy metabolism of Pettenkofer, Rubner, Voit, and their followers. Many other topics he touches briefly, passing rapidly from one to another, in contrast to the detailed analysis by Fruton of a smaller number of major topics.

Fruton in his introduction comments on the tendency of historians, especially of scientists turned historians, to judge other scientists as "good guys" or as "bad guys," depending on whether they were or were not working along the line of development that later proved successful. The scrupulous historian will strive to avoid such bias, but no one can be altogether free of it. Florkin's treatment of what he calls "the dark age of biocolloidology" raises questions of this sort. I grew up as a student in the latter part of that "dark age," when the conflict was sharp between the colloid chemists, who sought to explain the behavior of proteins in terms of adsorption, and aggregation of particles, and the chemists, such as T. B. Osborne, Jacques Loeb, S. P. L. Sörensen, and E. J. Cohn, who held that proteins were genuine but large molecules, to be understood by applying the well-known laws of organic and physical chemistry. As a student of Cohn's I became, of course, a strong adherent of the latter view, which has proved in the end to be victorious. Nevertheless I believe that Florkin, in portraying these controversies, makes them appear a little too much like a struggle between the forces of darkness and those of light. The colloid chemists, after all, were attempting to explain experimentally established but complicated phenomena, in an era of much ignorance (by present-day standards) and great confusion in the study of macromolecular systems. Not only the colloid chemists but the organic chemists, including the great Emil Fischer, were unwilling to believe in the existence of really large molecules, held together by covalent bonds. Thus the resistance to the "chemical" view of such molecules as proteins was quite understandable, given the prevailing scientific background of the time. The greatest weakness of many of the colloid chemists, I believe, was that their theories were sufficiently vague and flexible to accommodate all sorts of experimental facts; they were not, in Karl Popper's sense, falsifiable. In any case Svedberg, the greatest of the 20th-century colloid chemists, later became the foremost champion of the view that proteins were definite molecules, as Florkin indeed points out.

This criticism of one small aspect of Florkin's book should not obscure the value of the total enterprise; those concerned with the development of biochemistry will look forward eagerly to the later volumes.

Those like myself who have been conducting seminars in the history of biochemistry will find these books valuable. Fruton's book in particular has provided me, for the first time, with a text that can serve as a core around which other aspects of the seminar can be built. For these purposes, I think, it needs to be supplemented with biographical material on major investigators, and of course with study of original sources. In any case the appearance of these books is a major event for those who are concerned with understanding the development of this area of science, which is now of such central importance to the whole of biology.

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Meyerhof and Successors

Molecular Bioenergetics and Macromolecular Biochemistry. A symposium, Heidelberg, July 1970. H. H. WEBER, Ed. Springer-Verlag, New York, 1972. vi, 198 pp., illus. $25.10.

In July of 1970 a symposium was held in honor of Otto Meyerhof at his place of work. The time was chosen to coincide approximately with the 20th anniversary of Meyerhof's death and with the creation of a Meyerhof chair at the Weizmann Institute of Science in Rehovot, Israel. The proceedings have been published to make it possible "for the admirers of Meyerhof who were not able to attend the symposium in person, to be present in spirit." Since I belong to the large group of admirers of Otto Meyerhof, having participated in his 65th birthday celebration in 1949, I undertook to review this little book. I am glad I did.

The book starts with a fascinating account of Meyerhof's work and life by H. H. Weber. Meyerhof was actively interested in philosophy and the arts (he wrote poetry until his last year of life). His imaginative genius led him to correlate heat measurements with chemical changes in muscle, studies which mark the beginning of modern muscle biochemistry and led to the award of the Nobel prize in 1922. At the time Meyerhof was only 38 years old and still an assistant at the University of Kiel. His later work in Berlin and after 1929 in Heidelberg attracted a large number of students who later became leaders in the field of biochemistry. Among them are Ochoa, Lipmann, Nachmansohn, and Blaschko, participants in this symposium.

It is only regrettable that Weber's fascinating account of Meyerhof's work and personality is written in German and thus lost to the majority of our present biochemistry students, who no longer need to pass language examinations.

An excellent review of "Meyerhof's aldolase—35 years later" is presented by B. L. Horecker. It is fascinating to follow the developments which started with the discovery of aldolase in 1934 and culminated in the sophisticated current approaches to the mechanism of action of this key enzyme of glycolysis, which is responsible for the cleavage of the hexose to trioses.

Meyerhof's approach to the resolution of the glycolytic process has inspired many other investigators. Feodor Lynen's brilliant account of the multienzyme complexes responsible for the synthesis of fatty acids and of methyl salicylate is another contribution that our Germanless graduate students will have to miss.

Two famous Meyerhof students, S. Ochoa and F. Lipmann, contribute papers on polypeptide synthesis. Ochoa gives a detailed, experimentally documented account of the ribosomal factors in polypeptide chain initiation. The factors F_1, F_2, and F_3 should not be confused with similarly named factors participating in oxidative phosphorylation. But the similarity points to the fact that these processes have complexity in common. Lipmann, who is convinced that the complex process of present-day protein biosynthesis has been preceded by simpler ones, has turned to the study of polypeptide synthesis that is not aided by nucleic acids. The biosynthesis of gramicidin S and tyrocidine is described as taking place by amino acid polymerization on multienzyme complexes from protein-bound amino acyl thioesters.

On the second day of the symposium scientific grandsons (and granddaughters) of Meyerhof participated. The first two papers, by K. C. Holmes and A. Weber, are on the molecular structure and physiological regulation of the actomyosin system. They are excellent summaries of our present knowledge in this important area of biochemistry. L. Sachs, the holder of the Meyerhof chair in Rehovot, presents his findings on the relationship of cell surface changes and malignancy (for example, the response to concanavalin A) and raises the question of the genetic basis of malignant cell transformation.

The third day of the symposium was devoted to ion translocations and excitable membranes. R. Winkler and M. Eigen discuss the two classes of alkali-ion carriers: the neutral macrocyclic compounds (such as valinomycin), which selectively combine with a charged alkali-ion and therefore respond to an electric field, and the charged open-chain compounds (such as nigericin), which participate in an electrically neutral transport of ions. Experimental data on the use of murexide for the study of alkali-ion complexes and the interaction of monactin with Na^+ are presented. The chapter closes with a list of valuable conclusions about carrier molecules and a list of "problems to be solved."

A thorough review of the problem of the Ca^{2+} pump of sarcoplasmic reticulum and particularly the reversal of the pump action resulting in generation of adenosine triphosphate is presented by W. Hasselbach.

In the last chapter D. Nachmansohn lucidly states his views in favor of acetylcholin as an intracellular trigger which initiates and controls the permeability changes and ion movements during electrical activity.