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Biochemistry and the Historian

Molecules and Life. JOSEPH S. FRUTON (Wiley-Interscience, New York, 1972). Pp. 579. £9·90.

Biochemistry presents a formidable challenge to historians of science. The quantity of research carried out within the bounds of this field, the scope of its subject, the insights it provides concerning the nature of life itself, the implications of its findings for human welfare, all place it among the dominant modern sciences. Historians of science can hardly hope to describe adequately the development of science during this century without including it. Yet these same characteristics make it arduous for the historian who is not himself a specialist to acquire a comprehensive grasp of the history of the subject, and even more difficult to teach it clearly and succinctly to the diverse audiences he must attempt to reach. Modern biochemistry may be less esoteric than modern physics, but its nature is so intricate, so bound up with the immense array of compounds, reactions, and biological processes it has revealed, that to simplify it by limiting attention to the discovery of basic principles alone is to miss the very quality which has made it the scene of such extensive activity.

Perhaps in part because of this dilemma, but also because the dramatic successes which have placed biochemisty in the centre of attention among the biological sciences occurred very recently, relatively little has been written concerning the history of this science. Fritz Lieben's *Geschichte der physiologischen Chemie* (Leipzig, 1935) is usually cited as the only lengthy treatment. Happily the situation has begun to change; within the past decade a number of promising starts toward a fuller understanding of the subject have been made. In 1966 David Keilin's *The history of cell respiration and cytochrome*[1] appeared posthumously. Although Keilin oriented his account around the background to his own discovery of the cytochrome respiratory pigments, he took a broad view of that background, including perceptive discussions of concepts of respiration from Galen to Lavoisier, controversies over fermentation during the nineteenth century, the question of whether respiration occurs in the blood or the tissues, and other topics. Similarly Dorothy Needham has produced an extensive historical treatment of an area of biochemistry in which she herself made major contributions. Her *Machina carnis: the biochemistry of muscular contraction in its historical development*[2] is an authoritative, encyclopaedic account which should serve for a long time as the standard reference on the topic. John T. Edsall has written two valuable and thoughtful articles, one on the development of the concept that proteins are macromolecules, the other on the evolution between 1850 and 1928 of knowledge of the functional adaptation of blood and haemoglobin.[3] In a broader vein, the Belgian biochemist Marcel Florkin is writing a multi-volume *History of biochemistry*. The first volume,[4] which appeared in 1972, is divided into two parts, "Proto-biochemistry" and "From proto-biochemistry to biochemistry". As these titles suggest, this volume deals principally with events prior to the formation of biochemistry as a formal science, though it includes selected twentieth century discussions as well.

The preceding works may suggest that the history of biochemistry is a subject handled most readily by biochemists rather than by historians of science, but a few of the latter have also turned their attention to this field. Mikuláš Teich has written several short but penetrating essays highlighting crucial issues.[5] Teich has sought to define the most general phases in the origin and development of biochemistry; to demonstrate its interdependence with industrial concerns such as brewing and the production of synthetic dyes; and to delineate the relation of biochemistry to broad biological generalizations such as the cell theory. Robert Olby has written on the events surrounding the discovery of the double helix structure of DNA, focusing on the role of Francis Crick.[6] Robert Kohler has concentrated on the period 1890 to 1920 and the departures which set the newly emerging field of 'biochemistry' off from the 'physiological chemistry' which preceded it. The critical shift, according to Kohler, was the replacement of the idea that 'living protoplasm' is the source of all chemical activities within cells, by the theory that a specific enzyme catalyzes each reaction. While involving many factors, that change turned particularly on the response to Buchner's discovery of cell-free fermentation. In a series of very interesting articles Kohler has demonstrated the importance of immunological investigations for Buchner's work, examined the reactions to Buchner's conclusions by scientists in different biological fields, and pointed out some of the sociological dimensions of the formation of a 'new' scientific field.[7]

Collectively these studies have already illuminated a number of key issues and events in the history of biochemistry and of the earlier investigation of phenomena which came to be included within it. More important, they represent promising base points for future examinations of the subject. So far, however, they remain exploratory tracks into a vast unsurveyed territory. Meanwhile one book has appeared which has successfully mapped large regions of that area. Joseph Fruton carefully entitled his book *Molecules and life: historical essays on the interplay of chemistry and biology*. He did not intend it to be a history of biochemistry as such. Rather, he defines his topic as an examination of "some of the efforts, during about 1800–1950, to study the chemistry of living organisms". Not only does he leave out some of the 'tracks' along which biochemists have moved, but includes discussions of a number of developments in fields of science outside the conventional boundaries of biochemistry. A large portion of the book deals with the period before biochemistry existed as a distinct field. Nevertheless, the five general topics whose history he traces cover so much of the central concerns of biochemists that the book gives a coherent, if not exhaustive, view of the scope of the field during its first fifty years.

The first essay, "From ferments to enzymes", traces the history of concepts of fermentation from earliest times until Lavoisier formulated an equation for the basic reaction of the alcoholic fermentation of sugar; it summarizes the investigations which led Schwann, Cagniard-Latour, and Kützing each to infer that micro-organisms are necessary for fermentation, and the rejection of this view by Liebig; it portrays vividly the debates between Pasteur and Berthelot, during which Pasteur held the field for the belief that fermentation is indissolubly linked with the processes of living organisms; it ends with the overthrow of that view through Buchner's demonstration. The central events in this narrative are familiar, but Dr Fruton has given one of the best accounts of them available. What makes his version especially valuable is his careful attention to related, though less dramatic developments. By describing the successive discoveries of other biological reactions ascribed to ferments—in particular to the actions of diastase, pepsin, emulsin, invertase, trypsin, and urease—during the nineteenth century, Fruton prepares the reader to see that Buchner's discovery of cell-free fermentation not only proved the chemical nature of a key 'vital' process, but also brought the study of alcoholic fermentation "into the stream of enzyme research". Buchner's achievement was "a matter of improved technique rather than new theoretical insight", because the theoretical conceptions involved had already been developed through these other cases.

The second essay, on "The nature of proteins", is an impressive display of the continuity of investigations concerning a particular set of problems for more than a century and a half. Fruton begins with the methods for extracting and identifying fibrin, albumin, and casein which led, at the beginning of the nineteenth century, to the conception of a general class of 'albuminoid' substances. He follows the rise and fall of Mulder's 'proteine' theory and the confusion which arose in the decades after 1850 because of the great variety of products chemists obtained by decomposing proteins. He shows how an appreciation of the great diversity of individual proteins emerged over the same period. He explains the importance of the crystallization of proteins and the factors which nevertheless fostered, at the beginning of the twentieth century, the belief that proteins are colloids of indefinite chemical composition. Fruton emphasizes the significance of the work of Emil Fischer, who demonstrated through syntheses of polypeptides that proteins are chains of amino acids joined by peptide type bonds, although he also gives attention to alternative theories of protein structure proposed before and after Fischer's work. He depicts the many partially successful efforts to identify all of the amino acids in a given protein before the method of chromatography resolved that problem. The culmination of the long history of research on protein Fruton sees in the work of Frederick Sanger, which established the amino acid sequence of insulin by partial decomposition and the identification of end groups. He stresses the analogy between the determination of the positions of the amino acids in a protein molecule and the determination of the arrangement of the atoms in a smaller molecule by the methods of classical organic chemistry.

In this essay several of the main themes of *Molecules and life* become evident. Although Fruton gives considerable attention throughout to the theoretical conceptions of the scientists involved in these studies, he always regards the development of new experimental methods as the decisive factors. The first classifications of 'albuminoids' resulted from the methods of extraction and the reagents which provided the definitions of their properties. The first 'proteine' theory arose from the application of elementary analysis to these substances. The individuality of proteins was recognized when the method of 'salting out' began to be used to separate them. The identification of amino acids as the basic 'building blocks' of proteins depended upon the preference eventually established for mild hydrolysis as the method of decomposition. The acceptance of the protein theory of enzymes after many decades of uncertainty was due to the successful crystallization of enzymes. Chromatography made possible the complete definition of the composition of proteins. Fruton accords theoretical speculation a meaningful role, repeatedly pointing out situations in which it stimulated fruitful research even though later proven inadequate; but he insists over and over that such concepts were ordinarily inconclusive and that the debates they evoked were always resolved through new means to identify specific chemical substances and their reactions. Historians who view the history of science as a form of intellectual history might prefer to attribute a more directive role to conceptual presuppositions, theories, and the posing of problems. Perhaps Fruton has somewhat underrated their significance. As a biochemist who has spent many years in the laboratory, he may be predisposed to defend the primacy of methods. His position, however, cannot be lightly refuted. Historians of science who do not have extensive research experience are apt to be equally predisposed to focus on concepts, which they can treat more satisfyingly on paper, and to find methods less interesting.

"From nuclein to the double helix" traces what has become the best-known story in the recent history of the biological sciences. In keeping with his general approach, however, Fruton's emphasis diverges from other accounts. Although he accords due importance to the dramatic announcement in 1953 by Crick and Watson of their model of the structure of DNA, he gives less attention to this 'break-through' than to the long preceding history of the characterization of the chemistry of the nucleic acids. He describes the ambiguities left by Miescher's original analyses of nuclein, and the efforts of

Hoppe-Seyler, Kossel and others to distinguish between the nucleic acid and protein portions of nuclein. He follows the working out of the chemistry of each of the components—the purine and pyrimidine bases, the ribose and deoxyribose units—and of the positions of the linkages between these units and the phosphate groups. He elucidates the reasoning which led chemists to assume that the basic nucleic acid unit was a tetranucleotide, and the way in which this conclusion led to theories of periodicity. He describes the accumulating evidence that DNA and RNA were very long fibrous molecules, and stresses the significance of the analyses of Chargaff which showed that there is no uniformity of base composition in DNA, but that the ratios of purines to pyrimadines, of adenine to thymine, and of guanine to cytosine were nearly 1:1. By this time the double helix proposal of Crick and Watson appears as the logical, though brilliant outcome of a long tradition of investigation. Again the emergence or application of new chemical methods appears as the dynamic factor in the story, although Fruton does identify mental presuppositions such as the tendency of chemists to transfer to nucleic acids their conceptions of the nature of proteins.

The last two essays are especially intricate. "Intracellular respiration" begins with the respiratory theory of Lavoisier. It details the manner in which respiratory combustion came to be regarded, by the late nineteenth century, as an intracellular phenomenon; traces the chemical and spectroscopic investigations which established that haemoglobin is the carrier of oxygen in the blood; describes the numerous theories proposed between 1840 and the early twentieth century to explain how the respiratory substances, which are ordinarily inert at body temperature, are oxidized within the organism; follows the step-by-step identification of the substrates and reactions comprising alcoholic and lactic fermentation, and oxidative glycolysis; and elucidates the emergence of the conception that these reactions are linked to phosphorylation reactions by which the released energy of the former is stored in high energy bonds. "Pathways of chemical change" is about concepts and investigations of the assimilation of nutrient substances to the animal body and the metabolic decomposition of the body constituents. After recounting early nineteenth century views, Fruton describes Claude Bernard's discoveries concerning the glycogen function of the liver as the crucial initial demonstration that animals can perform synthetic reactions. He then follows the subsequent efforts to specify the chemistry of the interconversions of glycogen and sugar. He traces from 1800 to recent times the investigation of the relation between proteins and urea and describes the later studies of the metabolism of amino acids, all of which culminated in Hans Krebs's formulation of the ornithine cycle in 1932. This achievement marked a new stage in biochemical thought, according to Fruton, because for the first time a biochemical synthesis was explained in terms of chemical reactions identified in the biological system itself, rather than deduced from the chemical behaviour of supposed reactants. That methodological advance appears particularly important from the standpoint of *Molecules and life*, because one of its persistent themes is that chemists repeatedly proposed theories of biological processes derived from chemical knowledge—theories which inevitably proved inadequate to the biological complexities. While treating the metabolism of fatty acids Fruton depicts the great advantages which the use of radioactive isotopes brought after 1935 to the task of working out the intermediary reactions. As examples of the way in which isotopes facilitated the tracing of the syntheses of complex molecules in organisms, he describes the investigations which determined the sources of the constituent atoms of cholesterol and of porphyrin. These two essays are so replete with descriptions of specific compounds and reactions that the general reader will find them hard going; but the detail is essential to Fruton's purpose, which is to show that conceptual models of respiratory and metabolic pathways were never conclusive until the individual substrate molecules and their reactions had been determined, and the specific enzymes responsible for the reactions identified.

Molecules and life inevitably treats some topics which have already been discussed in other historical studies. In some of these cases it adds no novel interpretations, although Fruton almost always returns to the original sources and gives a fresh discussion. For much of the ground he covers, however, he has provided the first rigorous historical account, and the amount of material he has assembled for the task is truly impressive. Future historians may improve upon the discussion of particular episodes, but it will be difficult ever to supersede the sustained high quality of his synthesis of subjects of such immense scope. I believe that one of the most significant contributions he has made is to have treated evenly, with equal seriousness and insight, the investigations and thought of scientists from the beginning of the nineteenth century all the way to the very near past. One finds in this book no reflection of the attitude, common among present scientists, that the earlier pioneers worked at a less exacting intellectual or experimental level than those of today. Consequently the book achieves an end which historians of science have long sought—the merging of the history of science with modern science itself. Fruton attains this result not by subjecting the past to presentist evaluation, but by tracing the past forward until it reaches the present.

Fruton has directed his book both at "students of the biochemical sciences" and at historians of science. For the former the book poses the challenge that they stretch their awareness of the backgrounds of their own concerns much further into the past than they are accustomed to consider relevant to their work. For the historians of science the challenges are more daunting. On a first reading the book is liable to appear to them so densely packed with details that the main threads are hard to follow. Closer examination reveals, however, that far from being cluttered with detail, this book contains masterfully compressed, economical descriptions; details are used sparingly and with disciplined selectivity. The intricacy is inherent in the themes that are developed. One may object that the book is nonetheless too complicated to use in the teaching of general history of science. That may be true, but is tantamount to admitting that the history of science cannot hope to portray adequately the development of recent science. It seems evident that the complexity displayed here is both representative of the nature of modern science and the only reason that it can be the kind of activity which has absorbed the efforts of hundreds of participants. Undoubtedly summary versions of the main themes elucidated in this book can and will be incorporated into more general historical texts, and they will usefully fill a gap; but the elimination of detail in such accounts will entail a corresponding loss of appreciation of the characteristic nature of the historical movement in this area of science.

Some historians of science will probably object to the very nature of Fruton's venture. To the recent advocates of the examination of the social and cultural milieu of scientific activity, the formation of scientific communities, their institutional bases, and related factors, *Molecules and life* may appear to be another example of the kind of traditional history of science they wish to transcend. In general I am in sympathy with many of these calls for 'broader' approaches; what this book forcefully demonstrates to me, however, is that we cannot do without the careful description of the structure and development of scientific investigation itself. Far from being outmoded or worn out, it is a task which is only well under way. Far from an alternative to more socially oriented interpretations, books such as this one are an essential prerequisite to their success. Once we understand the structure and movement of a given area of science we can explore meaningfully the concomitant circumstances which conditioned its growth. Without that understanding we shall be in danger of weaving sophisticated backgrounds which have no well-defined foregrounds.

Finally *Molecules and life* stands as a challenge to the independence of the newly emergent professional historians of science who have been striving to form an autonomous discipline. Dr Fruton draws so heavily upon his thorough knowledge of his field that it is hard to see how anyone but a biochemist could have written this book. To acknowledge the necessity for books of this type is to admit the continued dependence of the history of science upon the contributions of scientists. That conclusion is, I believe, a cause for hope rather than for alarm. The intellectual demands made by the history of science are more than most of us as individuals can fulfill. To do the subject fully one must be a scientist, historian, philosopher, linguist and sociologist. Since few of us are good at all these things, the health of the field will, I think, always owe as much to those who examine it from each of these fields as to those who are trained within the mainstream of the new profession. It will be very desirable if Dr Fruton's book encourages other scientists to look seriously at the past development of their own fields. They should be forewarned, however, that the task is onerous. It is only because he has steeped himself as thoroughly in the history of his science as he has in its practice that Dr Fruton has produced a work of value both to historians and to scientists.

In writing this review I am conscious of the possibility that I may be somewhat inclined to view this book sympathetically because I had the opportunity to read and criticize it in manuscript form and therefore have a kind of prior association with it. Rereading the book several years later under quite different circumstances, however, has convinced me that my initial favourable impressions were sound, and that, if anything, I had not then fully appreciated the magnitude of the achievement. I am reasonably confident that my evaluation is not unduly coloured by the pleasure of having seen Dr Fruton frequently while he was at work on *Molecules and life*.

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