PRINCIPLES OF BIOCHEMISTRY

SIXTH EDITION

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Philip Handler, Ph.D.
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PREFACE

The preparation of the first edition of this book was initiated more than 25 years ago. Even a casual comparison of the present version with the first edition will make strikingly evident the remarkable advance in the sophistication and profundity of biochemical understanding that has occurred during the lifetime of this book. The explosive growth of biochemistry has resulted not only in an immense multiplication of knowledge in those areas that were already traditional subjects of biochemical studies, but also in the development of understanding of numerous biological structures and processes which had previously been inaccessible to biochemical investigation. That biochemistry has become the language for much of biology is evident in the great diversity of topics considered in the introductory chapter, "The Scope of Biochemistry." In retrospect, it can be seen that understanding progressed in an orderly, logical manner: the simplest, most general aspects were explored first; the more complex, subtle, and refined phenomena were examined when this became possible. The boundaries, if any, that distinguish biochemistry from much of the rest of biology have become entirely arbitrary. Biochemistry is not only the very stuff and language of cell biology, immunology, microbiology, physiology, pharmacology, pathology, and genetics, it is also the rational language for discourse in ecology, clinical medicine, and agriculture.

The goal of this book has continued to be an exposition of the principles of biochemistry as reflected in most of the major fields which are of general interest to all students of biochemistry, albeit with primary emphasis on the biochemistry of mammals, particularly of man. Nevertheless, as in earlier editions, considerable attention has been devoted to various aspects of the biochemistry of nonmammalian organisms. In numerous instances, this reflects the fact that many fundamental processes that occur in all species are more completely understood because of studies of those simpler organisms that are particularly suitable for such investigation. A few processes, such as the synthesis of some amino acids and the photosynthesis of carbohydrates, are of such significance to all of biology that, although they do not occur in mammals, they are here presented in separate chapters. These subjects could conceivably be ignored by medical students, but studied profitably by other students of biochemistry.

Several unusually large subject areas have been divided into separate chapters, e.g., biological oxidations, aspects of carbohydrate and amino acid metabolism, and the components of blood. These subdivisions of larger areas provide opportunities for the assignment and study of individual chapters by those seeking more detailed understanding of specific segments of biochemical knowledge with particular relevance to their major scholarship goals. We recognize that not all topics here considered can be included in all courses in biochemistry. The very growth of the subject matter necessitates that formal presentations of biochemistry now be appropriately targeted towards the relevant needs of students with very different professional and scholarly objectives. It is also self-evident that not all topics in this text can be explored in an initial survey course in biochemistry. It is our hope that, in later studies, students will seek to broaden and deepen their knowledge of other areas of biochemistry. As an example, the beginning student need only be familiar with the material on biological oxidations in Chap. 12; the more specialized topics in Chap. 13 can serve for later studies and for reference.

Some biochemical processes proceed somewhat differently in nonmammalian species. Consideration of these aspects of comparative biochemistry is included when it is thought that their comprehension affords a better appreciation of the mammalian systems. Occasionally, material of this nature is printed in smaller type in order not to interrupt the flow of the principal themes of the chapter. Similarly, a limited selection of pathological aberrations of normal processes is presented, primarily as natural experiments, understanding of which illuminates the normal situation.

The rapid growth of biochemical knowledge and the increasing difficulty in distinguishing the boundaries between biochemistry and the other biological sciences constituted serious challenges to the goal of completing a reasonably up-to-date sixth edition without an inordinate hiatus between editions. The task of meeting the schedule for a new edition has been greatly facilitated by the welcome addition of two new authors. More importantly, this has also resulted in new approaches to the structuring and writing of several individual chapters as the new authors accepted assignments for the initial preparation of various chapters. As in the past, all chapters were circulated among, criticized by, or even rewritten by all of the other authors, so that we continue to take collective responsibility for the content of the entire work.

The extraordinary progress of biochemistry itself required the complete rewriting of more than 75 percent of the total text. This is evident in the increased understanding of the mechanisms of biological phenomena at a molecular level, encompassing such areas as the structure of proteins, the mechanism of enzyme action, aspects of nucleic acid and protein synthesis including both their genetic significance and their pathological aberrations, the details of metabolic regulation, the composition and role of various cellular organelles and membranes, bioenergetics, the basis of muscle contraction, the structures and functioning of nerves and connective tissue, and the mechanism of hormone action. All chapters that have not been completely rewritten have been extensively revised. Four new chapters, those on "The Prostaglandins," "Viruses," "Immunochemistry and the Complement System," and "The Thymus," give deserved recognition to the increasing contributions of the fundamental knowledge and tools of biochemistry to other disciplines of the biological sciences.

The effort to compress the ever growing body of biochemical information and to select those topics deemed to be of major importance has been a serious challenge to the authors. Reluctantly, we have found it necessary to delete much of the historical background and to present ever less description of the experimental bases for the conclusions cited. We hope that the limited material devoted to descriptions of specific types of experimental procedures, and periodic references to their use, will enable the student to develop some grasp of how biochemical knowledge has been derived. Particularly regrettable to us has been the enforced omission of the names of the many hundreds of scientists who have been responsible for the flourishing development of biochemistry.

Grateful acknowledgment is made to the numerous colleagues and friends who have contributed information and criticism in the preparation of this new edition as well as to those teachers and students who have made valuable suggestions and directed attention to occasional errors. We wish also to acknowledge the patient and pleasant cooperation and assistance provided by Mr. J. Dereck Jeffers and Ms. Alice Macnow, Editors, and Mr. Michael LaBarbera and Mr. Timothy Armstrong, Editing Supervisors, and to the staff assigned by the publisher for coordinating the diverse activities involved in the completion of this book.

Finally, and with deep appreciation, we wish to acknowledge the patience and supportive understanding of our wives during the many hours of scholarship in isolation required for the preparation and completion of this edition.

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CHAPTER 1

THE SCOPE OF BIOCHEMISTRY

In the early dawn of language, the word *life* was employed to characterize the condition of objects as diverse as grass, trees, insects, worms, birds, fish, and humans. Each proceeds through a life cycle, reproduces its own kind, and responds in a variety of ways to external stimuli. Over the course of a few millennia, "living" forms were classified, first in terms of characteristics visible to the unaided eye, i.e., their gross comparative anatomy, and later with the aid of the light microscope. In the early nineteenth century, Schleiden and Schwann recognized that all these forms were constructed of unit cells of rather similar dimensions and general appearance. This relatively primitive body of information, together with increased understanding of the fossil record, sufficed to permit formulation by Darwin of the most sweeping and compelling biological generalization of all, the concept of historic and continuing biological evolution.

Meanwhile, progress in the physical sciences led, in turn, to increasingly sophisticated questioning by students of biology. Identification of the major atmospheric gases was soon followed by demonstrating the use of oxygen and production of carbon dioxide by animals and the photosynthetic reversal of this relationship in green plants. The general statements of the laws of conservation of energy and matter applicable to the physical world were shown by Lavoisier and Laplace in 1785 to be equally valid in a biological system that they could examine experimentally. Isolation of increasing numbers of purified materials from living forms and recognition of the fact that all contained carbon gave birth to *organic chemistry*. This actually fortified vitalistic thinking until Wöhler synthesized urea in 1828, thereby demonstrating that carbon compounds need not necessarily be formed in living organisms. Formulation of the general principles of catalysis by Berzelius rapidly led to recognition that the ptyalin of saliva, pepsin of gastric juice, and amylase of sprouted malt were biological catalysts. Yeast was believed to be an inert catalyst at that time, and hence early studies of the chemistry of fermentation failed to contribute to the decline of vitalistic thinking. Indeed, it is ironic that chemical synthesis of ethanol, by Hennell, had preceded the synthesis of urea but did not serve as an equivalent philosophical milestone because the living nature of yeast failed to gain acceptance until the work of Pasteur.

Until the major laws of physics and chemistry governing the inanimate universe had been elucidated, it was not possible to formulate the more penetrating questions concerning the nature of life. These questions, which we shall consider shortly, were not expressed until the first quarter of the twentieth century. Meanwhile, inorganic, organic, and physical chemistry flourished, the laws of thermodynamics were enunciated, and it became possible to examine, in detail, whether living systems also obey the laws of physics and chemistry. The doctrine of evolution gained acceptance, the principles of genetic inheritance were formulated by Gregor Mendel, and the list of compounds obtained from living organisms grew ever larger. The conducting role of the nervous system was described and the role of glycogen as a storage form of glucose in liver and muscle was demonstrated by Claude Bernard, who also recognized the constancy of the *milieu interieur*. The germ theory of disease was established and systematic microbiology introduced.

At the turn of the century, Emil Fischer established the structures of many carbohydrates, learned to separate amino acids from hydrolysates of proteins, and initiated much of contemporary biochemical thought by recognizing the optical configurations of carbohydrates and amino acids and by demonstrating the specificity of enzymic action. In postulating the "lock-and-key" concept of enzymic action (Chap. 9), Fischer began the study of the relation of the topography of macromolecules to the phenomena of life. With these studies and the exploitation by Harden and Young (Chap. 14) of the accidental observation by the Buchner brothers that a cell-free extract of yeast could ferment glucose with the production of alcohol, modern biochemistry began. The term *biochemistry* was introduced by Carl Neuberg in 1903.

Ever since, information and understanding have been increasing exponentially. Intellectual curiosity and philosophical questions have given general direction to the course of these biochemical investigations. In large measure, however, the quickening tempo of this effort reflects not so much a fundamental human drive for self-understanding as the belief that the knowledge gained could improve agricultural practice and with it animal and human nutrition, as well as assist in the alleviation of human disease. In significant measure, these goals have been realized.

Research in biochemistry has been addressed to a series of major questions, each of which continues to command attention. These will be briefly considered below.

Of what chemical compounds are living things composed? A catalog of such compounds is a *sine qua non* for the understanding of life in chemical terms. New compounds are, however, continually being recognized, as in the course of investigations directed toward unraveling metabolic reaction sequences that start with a well-recognized chemical entity or by isolation of the naturally occurring substance responsible for some physiological event. The ubiquitous distribution of many of these compounds results in a high degree of similarity in the *qualitative* composition of most living organisms, with differences between these forms, as well as among their own tissues and organs, being primarily *quantitative*. These quantitative differences are paralleled generally by differences in functions and by the relative rates at which similar functions, processes, or reactions may proceed.

What are the structures of the macromolecules characteristic of living organisms? The pioneers of biochemistry recognized the presence in nature of substances they named proteins, nucleic acids, polysaccharides, and complex lipids. The rate of progress of biochemical understanding has, in no small part, been paced by the development of procedures to isolate and purify such materials. New physicochemical methods revealed molecular weights of from 10,000 to more than 100 million for individual substances. For years, the seemingly herculean task of establishing the complete structures of such molecules appeared to be experimentally unapproachable. However, development of a variety of new physical instruments including the ultracentrifuge, electrophoretic apparatus, recording spectrophotometers, spectropolarimeters, and amino acid analyzers helped reveal the general structures of these molecules. Improved analytical techniques and, in particular, diverse chromatographic methods permitted the separation and quantitative determination of the micro amounts of complex mixtures required to deduce the covalent structures among the building blocks of diverse macromolecules. With the development of x-ray crystallographic methods, detailed three-dimensional models of many smaller proteins and nucleic acids are now available, and there is a rapidly growing understanding of the forces by which these molecules, which would otherwise be long, thin fiberlike structures, fold themselves into highly specific compact structures. The biological functioning of these molecules is entirely dependent upon their three-dimensional structures.

Understanding of the structures of these large molecules is rapidly expanding, thereby providing the basis for a more penetrating insight into the mode of operation of enzymes, the structural basis for genetic phenomena, and the fine structure of living cells. Indeed, this is a major theme of this book.

How do enzymes accomplish their catalytic tasks? In the nineteenth century, degradation of proteins, starch, and fats to their smaller constituents in the digestive tract was recognized as being due to enzymic activity. That fermentation is also the result of such catalysis was later shown by the Buchners. Twenty years earlier, Kühne had coined the name *enzyme* (Gk., in yeast) to designate the unorganized "ferments," as distinguished from bacteria, which were also called ferments. The studies of Fischer on the specificity of enzymes were followed by the formulation by Michaelis and others of the elementary rules describing enzymic catalysis and by Sumner's isolation in 1926 of the enzyme urease as a crystalline protein. Since then, hundreds of pure enzymes, each more or less specific for one chemical reaction, have been isolated and many crystallized; each has proved to be a distinct, unique protein.

How these proteins function as catalysts is one of the central problems in biochemistry—and one of the oldest. In a sense, the question was first raised in 1800, when the Academy of the First French Republic offered a prize of one kilo of gold for a satisfactory answer to the question: What is the difference between "ferments" and the materials they are fermenting? The prize was never awarded. In all probability, those who posed this question would have been pleased to award the prize a century later to Emil Fischer, who, however, was aware of the superficiality of his understanding. In the time since, the phenomena operative in enzymic catalysis and their bases in protein structure have been revealed in considerable detail. This fascinating aspect of science, in many respects the heart of biochemistry, is the subject of Part Two of this book.

What substances are required to satisfy the nutritional requirements of man and other organisms, and what are the physiological roles of these compounds? The small catalog of these substances, now perhaps complete for human beings, is presented in Part Six. This knowledge is adequate to manage the nutritional affairs of mankind; the inadequate nutrition of much of humanity reflects failures of production and inequities of distribution, not lack of nutritional understanding.

In the course of studies of the nutrition of bacteria, powerful experimental tools were forged that have influenced all aspects of biochemical research. The ability to estimate bacterial growth quantitatively has been utilized as the basis of sensitive analytical procedures.* The fact that a given compound is an essential nutrient because the organism cannot accomplish its synthesis yet requires that compound for further metabolic transformations has been exploited in the elucidation both of metabolic pathways and of genetic mechanisms.

By what chemical processes are the materials of the diet transformed into the compounds characteristic of the cells of a given species? Study of the manifold individual events of metabolism was at the center of biochemical interest until comparatively recently and continues to demand attention. Rather large quantities of a small group of organic compounds are ingested daily. The growing child retains some of these as a collection of compounds that is rather different from the composition of the ingested mixture. Similarly, plants "ingest" only water, minerals, and CO_2 yet accumulate a remarkable ensemble of diverse compounds. Most of the carbon of the ingested food of the child is released to the expired air while the nitrogen appears in the urine as urea; the remarkably sensitive regulation of these processes is even more evident in adults, who maintain constant weight and composition while they process about a pound of mixed solids per day.

Since, in attempting to understand these processes, one cannot readily sample the reaction mixture, how can one ascertain the reactions to which ingested foodstuffs are subjected? This experimental impasse was broken by the availability of radioactive isotopes, particularly ^{14}C, and apparatus with which to measure their abundance. With the use of these tools, increased skill in the handling of tissue preparations in vitro, and the powerful separatory capabilities of chromatographic procedures an elaborate, interwoven network of metabolic pathways was quickly exposed. This task continues, although the outlines of most major processes appear to have been revealed, as described in Part Three.

How is the potential energy available from the oxidation of foodstuffs utilized to drive the manifold energy-requiring processes of the living cell? Among such processes, we need note only the synthesis of hundreds of new molecular species, intracellular accumulation of inorganic ions and organic compounds against concentration gradients, and the performance of mechanical work. The impossibility of utilizing thermal energy to accomplish useful work at constant temperature makes untenable a simple analogy between food-burning animals and fuel-burning heat engines. Understanding of the biological solution to this problem, coupling of the oxidation of carbohydrates and fats to the synthesis of one compound, adenosine triphosphate (Chaps. 10, 12, and 13), with subsequent utilization of the energy of this compound for virtually all endergonic processes, is cardinal to the understanding of living cells.

The corollary problem, elucidation of the mechanism by which light energy is harnessed to achieve fixation of CO_2 into carbohydrate, has been a challenging major question in its own right (Chap. 16). Understanding of the primary photochemical events and the subsequent reactions that lead to carbohydrate accumulation has expanded greatly in recent years.

What is the structure of a living cell, and how is it organized to conduct its characteristic chemical functions? The general topography of cells—an outer membrane, an inner nucleus, and numerous lesser bodies—was early revealed in the compound light microscope. Electron microscopy has provided much more detailed stereoscopic visualization of the finer structure: a network of microcanals, the endoplasmic reticulum, which lead from within the nucleus through the cytoplasm and occasionally to the cell exterior; large complex bodies, the mitochondria; numerous smaller dense bodies frequently attached to the reticulum; a system of microtubules, which is employed for diverse purposes; an unusual organization of fibers in the spindle apparatus of a dividing cell; and the double-layered structure of the cell membrane (Chap. 11). Isolation of concentrated preparations of each of these substructures, free of the remainder of the cell, revealed the partition of functions within the cell: the nucleus as the site of genetic control and cellular duplication; ribosomes as loci for protein synthesis; mitochondria as membranous structures in which oxidative metabolism generates adenosine triphosphate; the membranous endoplasmic reticulum as the site of metabolism of certain nonpolar molecules such as steroids; the cell membrane as the site of vectorially organized mechanisms for controlling the general electrolyte composition of the cytoplasm, bringing required nutrients into the cell proper (Chaps. 11 and 34) and possessing numerous specialized receptors that receive chemical messages from other cells or from the general environment; intracellular contractile fibers; a variety of highly specialized structures, each unique to a specific cell type; and the cytoplasm, a solution of hundreds of individual enzymes that direct the multitudinous reactions by which nutrients are converted into cell constituents. It is the sum of all these chemical activities that constitutes the "life" of the cell.

By what means do cells divide to yield identical daughter cells? What is the chemistry of inheritance? What is a gene and how does it function? No chapter in the history of science has unfolded with such great rapidity or engendered such widespread interest as the answers to these questions. Few hold deeper or more significant implications for our future. This is the subject of Chaps. 25 to 28.

It is the presence and activities of its complement of proteins that determine the form, organization, and functions of a cell, viz., its life. It follows that the genetic "instructions" to a cell must provide the information required to achieve the precise synthesis of the ensemble of proteins characteristic of that cell. This information is encoded in the structure of the very large molecules of deoxyribonucleic acid. Cell duplication requires perfect reproduction of these molecules with subsequent equal distribution of the information between the cells. Utilization of this information requires its transmittal from nucleus to the ribosomal protein factories. Changes in the chemical structure of deoxyribonucleic acid become evident as mutations in subsequent generations. How these processes operate has been disclosed largely by utilizing a nonpathogenic enterobacterium, *Escherichia coli*, and by study of the duplication of bacteriophages, bacterial viruses, each of which is a limited bit of genetic information wrapped in a specific protein coat and capable of self-duplication only by utilizing the synthetic apparatus of a living cell. The information thus gained has made intelligible the laws of genetics, the nature and basis of hereditary diseases, and the biochemical operation of the process of evolution.

Had evolution not been deduced earlier on other grounds, it would surely have become obvious to the biochemist. Whereas the unaided eye reveals the diversity of life, the qualitative answers to each of the foregoing questions are essentially identical for *all* living forms. The impressiveness of this oneness of the cardinal aspects of all forms of life is matched only by the remarkable manner in which subtle variations on these themes have given rise to the rich variety and abundance of living forms as well as the overall balanced activity of the total biosphere.

Since the life of a cell is the totality of thousands of different chemical reactions, each catalyzed by a specific enzyme, how are these synchronized into a harmonious whole? Clearly it is advantageous to the cell to match the pace of energy-yielding reactions to the requirement for that energy and to provide the requisite monomeric units (amino acids, nucleotides, sugars) at a rate commensurate with the demands for polymer synthesis (proteins, nucleic acids, polysaccharides). Investigation of the mechanisms by which such regulation occurs constitutes one of the latest chapters in biochemical research. Although details remain scanty, some of the outlines are clear; examples of such rate regulation can be found throughout this book. Included are arrangements analogous to both the negative and positive feedback systems of electronic engineering; these are intrinsic in the structures of some enzymes that participate in synthetic processes and help to assure a steady flow, but not a surplus, of necessary synthetic intermediates. In other instances, regulation involves repression or derepression of the synthesis of enzymes that participate in synthetic processes.

In the multicellular, multiple-organed vertebrate, not only must the diverse aspects of the metabolism of each cell be synchronized, but the various organs, muscle, liver, brain, etc., must also operate in harmony. Information concerning the metabolic state of muscle, for example, must be transmitted to the liver as required. In large part, this is the role of the endocrine system. Endocrine glands, responding to changes in the chemical composition of the blood, which in turn reflect changes in some tissue or organ, synthesize and release hormones, which are carried in the circulation to the target organs and there modulate specific cellular metabolic activities.

A host of compounds that are not the products of endocrine glands also serve to transmit information in other ways: the neurotransmitter substances that signal the arrival of a nervous impulse from nerve cell to nerve cell or nerve cell to muscle cell; the prostaglandins made in many organs and tissues, which modulate the activities of numerous other cell types; 1,25-dihydroxycholecalciferol, the synthesis of which requires consecutive reactions in at least two organs to become the active form of vitamin D, which facilitates Ca^{2+} absorption in the intestine; and cyclic adenylic acid, seemingly ubiquitous in living cells, which is formed from adenosine triphosphate by the membrane-bound enzyme *adenylate cyclase* upon receipt of some message from the cell's environment, e.g., a peptide hormone or a change in the nutritional properties of that environment, and then elicits a cellular response that varies with both the cell type and the message. Such processes will be encountered frequently in this book and form the major theme of Part Five.

How do the specialized cells of animal tissues and organs make their unique contributions to the total animal economy? Osteoblasts make bone, muscle cells contract, nerve cells conduct, kidney cells make urine, endocrine cells make hormones, all by mechanisms specific for these cell types. Because the systems involved are more readily accessible, biochemists were more successful in learning the generalities of how all cells live than in ascertaining the details of this group of specialized activities. More recently, this field of inquiry has proceeded apace, building upon the more general understanding gained earlier. Rather detailed understanding of the biochemistry of specialized cells is presented in Part Four and elsewhere. Much of future biochemical effort will be directed to expansion of such understanding.

How does an animal regulate the volume and composition of the fluids that constitute the environment of its cells and of the blood that interconnects them? The large body of information that has been gathered in this area of inquiry has contributed significantly to the management of diverse acute human disorders and to the achievements of modern surgery. The physiological mechanisms involved are extraordinarily sensitive and, as in critically engineered systems, frequently redundant. They have reached a high degree of perfection in human beings—and thus permit them to range the earth from the equator to the poles, from ocean depths to mountain peaks, and to survive despite enormous variations in the composition and quantity of the food and drink they ingest. These regulatory mechanisms are also discussed in Part Four.

Central to much of this aspect of vertebrate life are the physiology of the erythrocyte (Chap. 32) and the chemistry of hemoglobin, perhaps the most thoroughly studied of all proteins and our most detailed source of insight into the correlation of protein structure with physiological function (Chap. 31).

How is the genetic information in a totipotent, fertilized egg utilized to direct development of a differentiated organism? Thoughtful statement of this problem has been possible for decades; bits of information concerning chemical aspects of the developing embryos of chicks, sea urchins, and other species have been accumulated for many years. Only now, with deeper understanding of molecular genetic mechanisms, does it appear possible to attack this problem successfully. A growing literature describes various aspects of the mechanisms involved in the developmental changes observable in simple organisms, e.g., sporulation or cilia formation in bacteria, light-dependent formation of the photosynthetic apparatus in *Euglena*, etc. Nevertheless, this wondrous process cannot yet be described in a satisfying way. Although it offers a fertile field yet to be plowed, little information can be presented.

Accidental entry of microorganisms or foreign macromolecules into a mature animal evokes an "immune response" by which the invader is rendered harmless. How is the foreign nature of such materials "recognized" by the body and rendered innocuous? This process, the key to antibody production, has proved to be remarkably complex, requires participation of several types of cells, and is rapidly being disclosed. A summary will be found in Chap. 30.

By what mechanisms do cells "recognize" other cells? In the course of development there are countless instances in which cells of one type must "recognize" and closely unite with other, similar cells. In some instances this is necessary only to form a parenchymatous organ, e.g., liver; in others, a specific nerve cell must synapse with only one other specific nerve cell to form a tract leading from the periphery of the body to an area in the central nervous system. The basis for such cellular discrimination is now under extensive investigation. Closely related to the