General Biochemistry

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Preface

This book is largely based on a course in general biochemistry offered at Yale University. Intended primarily for candidates for the Ph.D. in the biological sciences and in chemistry, the course has also been attended by qualified college seniors, by students of medicine, and by postdoctoral research students in the medical sciences. The response to the lectures has strengthened our view that the teaching of biochemistry for its own sake, quite apart from its applications to medicine or agriculture, is an essential component in the scientific education of the biologist or the chemist. This book is offered, therefore, in the hope that it may prove useful to students who wish to examine the structure of modern biochemistry from a general point of view.

In some respects, the organization of the contents departs from the practice followed in the many admirable textbooks of biochemistry that have appeared in recent years. We can make no claim for a peculiar excellence in our arrangement of the subject matter, or in the selection of topics for emphasis. In beginning the book with an extensive discussion of protein chemistry, we have attempted to stress the central place of the proteins in the chemical activity of living matter. Also, these first chapters provide a review of several topics in elementary physical chemistry important for biochemists. The chapters on proteins are followed by a discussion of the general properties of enzymes, and of equilibria and rates in enzyme-catalyzed reactions. These sections of the book are intended to focus attention on the important role of the catalytic proteins in metabolism, and to sketch, for the student who lacks an adequate background in physical chemistry, the elementary principles of thermodynamics and kinetics as applied to biochemistry. The major portion of the book is devoted to a consideration of the problems of biochemical dynamics, with especial reference to biological oxidation and to the intermediate metabolism of carbohydrates, lipids, and proteins. The chapters on the chemical structure of carbohydrates and lipids are brief, since this material is usually well treated in courses in organic chemistry; the discussion offered here is intended to provide the minimum of structural biochemistry required for an understanding of the changes these substances undergo in biological systems. In the sections on intermediate metabolism, emphasis has been placed, whenever possible, on the individual enzymes and on the coupled enzyme-catalyzed reactions that are involved. Many biochemical processes cannot be discussed in these terms at present; we have attempted to indicate this wherever appropriate, and, in three of the final four chapters, reference is made to efforts to relate the metabolic role of inorganic ions, of hormones, and of vitamins to known enzyme-catalyzed reactions.

The inclusion of a relatively large number of bibliographic references is, in our opinion, essential in the presentation of subjects whose experimental basis is in rapid flux. This book will have served its purpose if it encourages the inquiring student to broaden his view of the subject through diligent study of the articles and books cited in the text. We hope that he will examine critically some of the original data, and not be content with the generalizations drawn from them. To emphasize the data alone would challenge only the student's memory; the generalizations are essential to capture his imagination, although, without the supporting experimental facts, emphasis on hypothesis invites superficiality. Within the limitations imposed by the requirement that this be a book of reasonable size, we have attempted, whenever possible, to balance facts against hypothesis. For several topics, we have found it expedient to do this by describing their historical development. Apart from its pedagogic advantages, the historical approach should give the student a sense of the dynamic in the growth of biochemistry. We believe it to be our duty to trace the background of present knowledge, since the successes and failures of the past emphasize the transitory nature of views now current and indicate the promise of the future.

In the preparation of this book we were fortunate in having the generous advice and encouragement of many kind friends. To mention all of them by name would make this preface unduly lengthy, but we must record our especial debt to Dr. A. Bendich, Prof. W. M. Clark, Prof. D. I. Hitchcock, Prof. C. N. H. Long, Prof. J. P. Peters, Prof. E. Racker, Prof. S. Ratner, and Dr. H. B. Vickery. In expressing to these individuals, and to others, our gratitude for their help, we do not wish to transfer to them any responsibility for the shortcomings that will be apparent to the critical reader; for any errors of omission or commission,

we are alone accountable. We appreciate the courtesy of many authors and publishers in giving us permission to quote or reproduce copyrighted material. We reserve our final though no less heartfelt thanks for the devoted assistance of Miss R. V. Brown, who typed the manuscript and checked the bibliography.

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1. The Scope and History of Biochemistry

The discipline called "biochemistry" deals with the study of (1) the nature of the chemical constituents of living matter and of chemical substances produced by living things, (2) the functions and transformations of these chemical entities in biological systems, and (3) the chemical and energetic changes associated with these transformations in the course of the activity of living matter. The ultimate goal of biochemistry is to describe the phenomena that distinguish the "living" from the "nonliving" in the language of chemistry and physics.

It will be seen at once that the first part of our definition falls within the scope of what is now termed organic chemistry. Indeed, in its original meaning, the term "organic chemistry" was intended to refer to the chemistry of "organized," or living, matter. A clear statement of this may be found in the *Lectures in Animal Chemistry,* first published in 1806, by the great Swedish chemist Jöns Jacob Berzelius (1779–1848):

> The part of physiology which describes the composition of living bodies, and the chemical processes which occur in them, is termed organic chemistry.

Implicit in this definition was the thought that the chemical substances produced by living things were fundamentally different from the "inorganic" materials found in inanimate matter; many distinguished chemists of that period held the view that these organic compounds were the result of the operation of "vital forces" and could not be synthesized artificially from inorganic substances. This view had to be abandoned, however, in the face of the successes of Friedrich Wöhler (1800–1882) in the artificial synthesis of urea (1828), of Hermann Kolbe (1818–1884) who first synthesized acetic acid in 1845, and especially of Marcellin Berthelot (1827–1907) from whose work synthetic organic chemistry received tremendous impetus during the middle of the last century. A major consequence of this development was a change in the definition of the scope of organic chemistry. Thus, August Kekulé (1829–1896) wrote in his famous textbook of organic chemistry, published in 1859–1860:

> We have come to the conviction that . . . no difference exists between organic and inorganic compounds. . . . We define organic chemistry therefore as the chemistry of the carbon compounds. . . . It must be emphasized that organic chemistry does not deal with the study of the chemical processes in the organs of plants or animals. This study forms the basis of physiological chemistry.

Increasing specialization of this kind is inevitable in the face of rapidly expanding knowledge; it must be stressed, however, that arbitrary divisions of science do not abolish the intimate interrelationships among the component disciplines—they can only obscure the essential unity of science. No student of biochemistry can enter upon this subject without adequate grounding in the methods and concepts of modern organic chemistry. Also, the student will do well to remember that organic chemistry is undergoing constant extension, revision, and refinement, and that these advances will influence the methods and concepts of biochemistry. A modern textbook of organic chemistry is therefore a valuable adjunct to the study of biochemistry. The treatises of Fieser and Fieser [1] and of Wheland [2] may be recommended for this purpose.

The second and third parts of our definition of the scope of biochemistry refer to the chemical dynamics of living matter, and here the tie to physiology, the study of the functions of living things, is obvious. In a very real sense, the problems that the biochemist seeks to solve are the problems of physiology, and many of the important discoveries that now fall within the scope of biochemistry were the outcome of the study of biological phenomena whose chemical aspects were only appreciated much later. Of particular importance were the accurate observations of skilled clinicians who studied the physiological dysfunctions of man. It must be added at once that the term "physiology," as used here, refers to the bodily or cellular functions not only of man, or other animals, but of plants and of microorganisms as well. Such a view of the field of physiology has frequently been denoted by the term "general physi-

[1] L. Fieser and M. Fieser, *Organic Chemistry*, 2nd Ed., Heath and Co., Boston, 1950.

[2] G. W. Wheland, *Advanced Organic Chemistry*, 2nd Ed., John Wiley & Sons, New York, 1949.

ology."[3] Though many men have contributed to the development of general physiology, the work and writings of Claude Bernard (1813–1878)[4] and of Louis Pasteur (1822–1895)[5] were pre-eminent in their influence. Perhaps the most important concept that emerged from the researches of Bernard, Pasteur, and their contemporaries was that, on the biochemical level, there is unity among the manifold forms of living matter. In the face of the fragmentary chemical knowledge of their time, this concept could only be dimly perceived; with the rise of modern biochemistry, during the past half-century, it has received extensive documentation. It is now clear that a chemical process studied in a yeast culture may illumine a comparable series of reactions in mammalian muscle; or the study of the respiratory pigments of invertebrates may provide basic data for the elucidation of a general mechanism of biological oxidation. Although there is much diversity in the chemical activities of different biological forms, it is becoming ever clearer that the fundamental biochemical reactions underlying cellular function exhibit a striking uniformity from the lowest to the most highly organized forms of life. In its subsequent historical development, therefore, a major section of "general physiology" has been transformed into "general biochemistry."

In the study of the functions of living things, one is confronted by physical phenomena (e.g., motion, light absorption, production of heat). It has long been the task of one area of general physiology, now sometimes called "biophysics," to study such phenomena. The growth of biochemistry has permitted, in many instances, the correlation of physical events in biological systems with chemical processes. The biochemist, therefore, must consider a physiological process not only in terms of the chemical nature of the substances that are involved in it, but also in terms of the physical relations among these substances, and of these substances to the environment. To do this adequately, he must call into play the body of knowledge known as "physical chemistry." In order to understand the energetic relationships in biological systems, an acquaintance with thermodynamics is essential, and no approach to the chemical dynamics of living things can be made without a knowledge of the kinetics of chemical reactions. Much of modern biochemistry has its foundations in the work of Josiah Willard Gibbs (1839–1903)[6]

[3] H. Davson, *Textbook of General Physiology,* J. and A. Churchill Ltd., London, 1951.

[4] J. M. D. Olmstead, *Claude Bernard,* Harper and Brothers, New York, 1938.

[5] R. J. Dubos, *Louis Pasteur,* Little, Brown and Co., Boston, 1950.

[6] L. P. Wheeler, *Josiah Willard Gibbs,* Yale University Press, New Haven, 1951.

on chemical thermodynamics, of Jacobus Henricus van't Hoff (1852–1911) on chemical kinetics, and of Svante Arrhenius (1859–1927) on electrolytic dissociation. Among the many excellent textbooks of physical chemistry are those of Glasstone [7] and Daniels; [8] valuable books on this subject, as applied to biochemical problems, are those of Clark [9] and of Bull.[10]

From the foregoing discussion of the scope of biochemistry, it will be clear that this field resists classification as a biological or a physical science. Not only does biochemistry cut across the artificial boundaries set up within chemistry and within biology—it also serves to link the physical with the animal and plant sciences. Many separate streams of knowledge thus nourish the growth of biochemistry, and its rapid development in recent decades is the direct consequence of the fruitful blending of many broad lines of experimental endeavor. For example, the newer knowledge of atomic structure and the resultant discovery of isotopes have provided the most powerful method yet devised for the study of chemical changes in intact animals, plants, or microorganisms. In the same way, purely biological studies on genetics and the artificial production of mutations also have led to the study of biochemical reactions from new points of view. These are but two recent examples of the cumulation of knowledge from different disciplines brought to bear on biochemical problems. The earlier history of biochemistry is replete with other examples.

Because of its successes in gaining a clearer understanding of the chemical activity of all forms of living matter, biochemistry has had many important applications in medicine and agriculture, and thus has contributed materially to human welfare. It is well to remember, however, that, though these practical benefits of biochemistry have been great, and promise to be greater, they are the result of studies largely undertaken for their own sake, rather than as conscious attempts to cure a disease or to increase a crop. The student of applied biochemistry (e.g., nutrition, chemical pharmacology) cannot go far in his field without a clear appreciation of the fundamental facts and principles of

[7] S. Glasstone, *Textbook of Physical Chemistry*, Van Nostrand Co., New York, 1940.

[8] F. Daniels, *Outlines of Physical Chemistry*, John Wiley & Sons, New York, 1948.

[9] W. M. Clark, *Topics in Physical Chemistry*, 2nd Ed., Williams and Wilkins Co., Baltimore, 1952.

[10] H. B. Bull, *Physical Biochemistry*, 2nd Ed., John Wiley & Sons, New York, 1951.

biochemistry, and, what is perhaps more important, of the gaps in biochemical knowledge that still remain to be filled.

Some Historical Aspects of Biochemistry

The origins of biochemistry may be traced to the writings of that turbulent upsetter of the *status quo,* Theophrastus Bombastus von Hohenheim (1493–1541), who gave himself the name Paracelsus. Paracelsus began his education in the mining region of Carinthia, and there he acquired a knowledge of the chemistry of his time. In general, the chemists of the early sixteenth century were of two classes: One group comprised the artisans employed in the mines, or in the working of metals, or in the pottery, glass, or dyeing industries. In the second group were the mystics and delightful charlatans who strove by obscure and occult means to transmute the baser metals to gold or silver, or to discover the elixir of life. Paracelsus got something from each of these groups, and, when he entered the field of medicine, he brought his chemistry with him.

The union of chemistry with medicine animated the work of many who followed Paracelsus, and who called their field "medical chemistry" (iatrochemistry). It cannot be said, however, that the scientific basis of biochemistry may be found in their writings. The real foundations are rather in the work of men of the second half of the eighteenth century, and among these the names of Carl Wilhelm Scheele (1742–1786) and of Antoine Lavoisier (1743–1794) are pre-eminent.[11]

Scheele, a Swedish pharmacist, was interested in the chemical composition of vegetable drugs, and of plant and animal materials in general. During his lifetime, he isolated a large number of new substances; among these were citric acid from lime juice, lactic acid from sour milk, tartaric acid from wine, malic acid from apples, and uric acid from urine. Also, by heating plant and animal fats with alkali, Scheele discovered glycerol. The substances that Scheele isolated from living matter and the many others obtained by his contemporaries had to remain the objects of curiosity until two important steps had been taken in the establishment of chemistry as a science. The first of these was the development of the concept of oxidation, by Lavoisier, and the second, the enunciation, in 1804, of the atomic theory by John Dalton (1766–1844). These, in turn, led to the development of the techniques of quantitative elementary analysis by Berzelius and by Justus

[11] D. McKie, *Antoine Lavoisier,* J. B. Lippincott Co., Philadelphia, 1936.

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von Liebig (1803–1873).[12] The analysis of the many products that had been isolated from plants and animals by 1850 showed them to contain carbon. As was already noted, the study of the structure of these compounds became the task of organic chemistry, and, by the end of the nineteenth century, synthetic organic chemists had made in the laboratory many of the compounds originally found in biological materials. At first only simple substances such as urea were synthesized, but, by 1885, nature had been successfully imitated in the synthesis of two plant dyes of complex structure—indigo and alizarin.

The experimental contributions of Liebig played an important part in the early development of biochemistry, and several of his books profoundly influenced subsequent efforts in this field. Of especial significance was his *Organic Chemistry in its Application to Physiology and Pathology,* published in 1842. The fragmentary data available to him at that time did not deter Liebig from extensive speculation as to the chemical basis of biological processes. For this reason, his book elicited from Berzelius the following comment, which has meaning even today:

> This easy kind of physiological chemistry is created at the writing desk and is the more dangerous, the more genius goes into its execution.

The high point in the development of structural biochemistry came in the work of Emil Fischer (1852–1919)[13] who, in the course of his scientific career, completely altered the direction of research on the chemistry of the principal organic components of living matter—the sugars, the fats, and the proteins. The decisive factor in Fischer's success was his skillful use of the techniques of organic chemistry to obtain from complex materials of unknown structure simpler chemical substances whose structure could be established, first by degradation, and then by synthesis. Much inconclusive work had been done by Fischer's predecessors on the chemistry of complex biochemical substances; it was his genius that set descriptive biochemistry upon the fruitful path it still follows.

Just as the roots of descriptive biochemistry lie in the researches of Scheele, the basis of dynamic biochemistry may clearly be found in the work of Lavoisier. In replacing the phlogiston theory of combustion by the concept of oxidation, Lavoisier also clarified the nature of animal respiration and the relation of this physiological phenomenon to the production of body heat. There are few sentences in the literature of biochemistry more dramatic in their impact than the following, taken from Lavoisier's memoir on heat, published in 1780:

[12] W. A. Shenstone, *Justus von Liebig,* The Macmillan Co., New York, 1895.
[13] M. O. Forster, *Trans. Chem. Soc.,* **117,** 1 (1920).

Respiration is therefore a combustion, slow it is true, but otherwise perfectly similar to that of charcoal.

The study of heat, during the first part of the nineteenth century, led to the formulation, in 1842, by Julius Robert Mayer (1814–1878), of the law of conservation of energy, which he explicitly applied to both living and nonliving things. The work of Mayer, of Hermann von Helmholtz (1821–1894), and of those who followed them led to the establishment of the science of thermodynamics, essential to the understanding of energy relationships in biological systems.

Although Lavoisier, in common with most of his contemporaries, thought that the combustion of foodstuffs occurred in the lungs, and Liebig later said that it took place in the blood, subsequent work, principally by Eduard Pflüger (1829–1910), showed clearly that the tissues were the site of this process. Much of the research in modern biochemistry has therefore been concerned with the mechanisms whereby the cells of tissues oxidize chemical substances derived from the food.

In addition to the process of respiration, another physiological phenomenon, that of digestion, occupied the attention of the pioneers of biochemistry. The initial advances in this field came from the work of John Baptist van Helmont (1577–1644), an iatrochemist, who sponsored a chemical theory of the digestion of food by animals. The decisive experimental evidence for this view came from the researches of Réné de Réaumur (1683–1757) and of Lazzaro Spallanzani (1729–1799). These investigations led to the study of the digestive enzymes by Theodor Schwann (1810–1882), Willy Kühne (1837–1900), and others.

The nineteenth century also witnessed the refinement of experimental surgery as a technique for the study of animal physiology. Through the efforts of François Magendie (1783–1855), Claude Bernard, Karl Ludwig (1816–1895), and their students, a firm groundwork was laid for the study of many physiological processes, and in the course of these efforts some of the chemical aspects of these processes became evident. By the end of the century, experimental surgery had reached a high point of development in the hands of Ivan Petrovich Pavlov (1849–1936). Many of the problems that the nineteenth century physiologists sought to solve came from clinical medicine and, in particular, from the study of the etiology of metabolic diseases. The production of experimental diabetes by the extirpation of the pancreas, described in 1889, is but one evidence of this close historical relation between physiology and medicine. Other clinical studies which profoundly influenced the development of physiology and of biochemistry dealt with goiter and Addison's disease. However, many dysfunctions of man, such as the deficiency diseases, still resisted fruitful experimental study during the last century. These had to await the further rise of biochemistry and the discovery of the vitamins.

Another biological process whose study had a decisive impact on the development of biochemistry was that of fermentation. In embarking, in 1857, upon the study of the chemical activities of microorganisms, Pasteur founded the science of microbiology and began a line of research that is actively pursued to this day. During the period 1900–1950 the close tie between microbiology and biochemistry was further strengthened through the work and influence of the Russian microbiologist Winogradsky, of the Dutch investigators led by Beijerinck and Kluyver,[14] and by Stephenson in England, among others. Some of the most convincing evidences of the biochemical unity of living matter have come from microbiological studies.[15,16,17]

Most of the great investigators cited above were aware of the disparity between the manifold chemical capacities of biological systems and the much more limited methods of the chemical laboratory. It was natural that in the early days of scientific chemistry this should have been taken as the expression of some vital force not observed in nonliving matter. Here biochemistry impinges upon philosophy, for the question "What is Life?" has been a compelling one throughout the history of human thought. With the discovery of the phenomenon of catalysis, during the first part of the nineteenth century, the assumption of a peculiarly biological chemical force became unnecessary, and Berzelius could write, in 1836:

> We have justifiable reason to suppose that, in living plants and animals, thousands of catalytic processes take place between the tissues and the fluids and result in the formation of the great number of dissimilar chemical compounds, for whose formation out of the common raw material, plant juice or blood, no probable cause could be assigned. The cause will perhaps in the future be discovered in the catalytic power of the organic tissues of which the organs of the living body consist.

The work of the past hundred years has shown that this "catalytic power" resides in a group of proteins which direct and control chemical reactions in biological systems—the enzymes. Some of the greatest suc-

[14] C. B. van Niel, *Bact. Revs.*, **13**, 161 (1949).

[15] E. F. Gale, *The Chemical Activities of Bacteria*, 3rd Ed., University Tutorial Press, London, 1951.

[16] M. Stephenson, *Bacterial Metabolism*, 3rd Ed., Longmans, Green and Co., London, 1949.

[17] J. W. Foster, *Chemical Activities of Fungi*, Academic Press, New York, 1949.

cesses of biochemistry have come from studies of the enzyme-catalyzed reactions involved in the degradation and formation of important chemical constituents of living matter, and it has become clear that enzyme chemistry is linked directly with every aspect of the biochemical dynamics of living cells.

Currently, the only comprehensive work on the history of biochemistry is that of Lieben.[18] A valuable account of the early development of biochemistry in the United States may be found in the book by Chittenden.[19] Other important books on the history of biochemistry are those of Browne[20] and of Bayliss.[21]

Some Comments on the Terms "Living" and "Nonliving"

In defining the scope of biochemistry its aim was stated to be the description, in the language of chemistry and physics, of the physiological phenomena observed in living matter. It appears desirable, in this introductory chapter, to examine briefly the meaning of the term "living" as distinguished from "nonliving." For a stimulating discussion of this question, see the article by Pirie.[22]

Since the middle of the nineteenth century, the phenomenon of "life" has been directly associated with morphological units termed "cells." The recognition of the cellular basis of living matter may be attributed to Matthias Jacob Schleiden (1804–1881) and to Theodor Schwann, although the experimental origins of the theory which they enunciated in 1838 may be traced to the work of the first microscopists (Hooke, Malpighi, Grew) in the seventeenth century. The concept of the cell as the structural unit of biological systems led to the famous dicta of Rudolf Virchow (1821–1902)—*Omnis cellula e cellula* (Every cell from a cell)—and of Pasteur—*Omne vivum e vivo* (Every living thing from a living thing). The studies of many cytologists (cf. Wilson,[23]

[18] F. Lieben, *Geschichte der Physiologischen Chemie,* Franz Deuticke, Leipzig und Wien, 1935.

[19] R. H. Chittenden, *The Development of Physiological Chemistry in the United States,* Chemical Catalog Co., New York, 1930.

[20] C. A. Browne, *A Source Book of Agricultural Chemistry,* Chronica Botanica Co., Waltham, 1944.

[21] W. M. Bayliss, *Principles of General Physiology,* 4th Ed., Longmans, Green and Co., London, 1924.

[22] N. W. Pirie, in J. Needham and D. E. Green, *Perspectives in Biochemistry,* Cambridge University Press, Cambridge, 1937.

[23] E. B. Wilson, *The Cell in Development and Heredity,* The Macmillan Co., New York, 1928.

Bourne [24]) have given experimental evidence of the transmission, from one biological organism to another, of structural units which enable the progeny to maintain a characteristic form and function.

It is customary to refer to the material of the cell as a jelly-like "protoplasm," but this is a vague term which includes numerous distinct morphological units such as the cell nucleus (diameter, 50–100 μ), mitochondria (diameter, 1–3 μ), and microsomes (diameter, 0.06–0.15 μ). Techniques are available for the physical separation of some of these cellular components, after rupture of the cell membrane, and they have been shown to be quite different in their chemical properties.[25] A living cell, therefore, is not an undifferentiated mass of protoplasm, but is rather an integrated multicomponent whole; many biological functions of the living cell depend on the maintenance of the integrity of this intracellular organization. It is this integration of structure that may be considered to serve as a basis for the differentiation of "living" from "nonliving" systems. However, as pointed out by Pirie,[22] the line of demarkation between the two is not a sharp one, and it is not possible at present to establish a completely satisfactory criterion for their differentiation.

Living cells may vary considerably in size and discernible complexity of intracellular structure, and these properties cannot be taken as criteria for their characteristic biological nature. Nor can adaptation, irritability, or motility be considered to be general properties of living systems, since there are many biological forms which, under certain conditions, do not exhibit the capacity to adapt to changes in their environment, to react to external stimuli, or to move. A more general biological property is that of growth, i.e., the assimilation of nutrients and their conversion into more "protoplasm," but it must be recalled that nonliving systems also exhibit the capacity to "grow." Perhaps the most striking evidence of this is the increase in the size of a crystal when placed in a supersaturated solution of the corresponding substance; here the presence of the seed leads to an organization of molecules or ions into a growing crystal lattice. Closely related to the biological phenomenon of growth is that of reproduction, which involves the formation of new cells and organisms, but here again, "self-reproducing" nonliving systems may be cited. For example, Jacques Loeb showed that it was possible to cause oil droplets to grow to a certain size and then to divide.

[24] G. H. Bourne, *Cytology and Cell Physiology,* 2nd Ed., Oxford University Press, London, 1951.

[25] W. C. Schneider and G. H. Hogeboom, *Cancer Research,* **11,** 1 (1951).

Also, living cells may be able to divide under one set of environmental conditions but are unable to do so under other circumstances.

All the above criteria for the differentiation of the "living" from the "nonliving" are related to another general property of biological systems, that of metabolism, which may be defined as the totality of the chemical changes undergone by the constituents of living matter. The occurrence of chemical change cannot, in itself, be a valid criterion of life, since many component reactions of cells have been made to proceed under the influence of enzymes obtained from cells or of particulate components (e.g., mitochondria) separated from broken cells.

Although no one of the properties usually associated with living matter is exclusively the attribute of biological systems, taken together they are an expression of a complexity of function which must be assumed to be the consequence of a remarkable structural organization of the working parts of each living cell. In metazoa, the individual cells are interdependent in form and function, and the products of the metabolic activity of one group of cells may affect the activity of other cells in the same organ, or may be transported by the fluids of the organism to the cells of another organ. At the multicellular level, therefore, account must be taken not only of the structural organization of the working parts of the individual cells but also of the integration of the activity of these cells.

In considering the chemical properties of biological systems, therefore, the biochemist studies the individual working parts of an extremely complex multicomponent structure. A large number and variety of chemical substances have been isolated from organs, or cells, or parts of cells. Certain compounds, or groups of compounds, are ubiquitous constituents of living cells. The most important of these components is water, which may represent between 70 and 90 per cent of the weight of a tissue. The cellular fluids contain a variety of inorganic ions; Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-, $HPO_4^=$, HCO_3^-, and $SO_4^=$ are the most abundant. The variety of organic chemicals obtained from living cells is extremely great. The most important of these are the proteins and substances chemically related to the proteins, the carbohydrates and related substances, and the lipids. In addition, there are numerous organic constituents of biological systems which cannot be fitted readily into one of these three categories. It is the purpose of this book to consider in turn the various chemical components isolated from living systems and to examine some of the available information concerning their metabolic interrelationships. As will be seen from the pages to follow, the chemical structure of many of the working parts of

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