BIOCHEMISTRY

EIGHTH EDITION

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With 289 illustrations, including 3 in color,
and 2 color plates

The C. V. Mosby Company
SAINT LOUIS, 1970

Eighth edition

Printed in the United States of America

Standard Book Number 8016-3728-7

Library of Congress Catalog Card Number 71-116594

Distributed in Great Britain by Henry Kimpton, London

PREFACE

The completion of the eighth edition of this book is both pleasant and sad. The sadness of the occasion is the reminder of the loss by death on June 10, 1966, of the original author, then coauthor, of the first seven editions, Dr. Israel Simon Kleiner. This edition is dedicated to his memory. He was indeed a talented and congenial coauthor as well as a friend and valued mentor. He is greatly missed.

The pleasant part of this occasion is the opportunity to welcome a new coauthor, Dr. Otto W. Neuhaus, a former colleague and longtime friend. Dr. Neuhaus brings to the book a point of view and a major interest complementary to that of the senior author. He is an experienced teacher with thorough, broad training in biochemistry under the late Professor Howard B. Lewis and Professor Lila Miller, both of the University of Michigan. Dr. Neuhaus also spent a valuable year as a NATO Research Fellow at the Laboratoire de Chimie Biologique, Université de Lille, Lille, France, studying with Professor G. Biserte.

In the present revision, we felt a reorganization of the text, with a somewhat different sequence of subject matter, was desirable. This need became urgent primarily because of the dramatic advances of the past decade in the biochemical-biologic sciences, specifically in molecular biology. The role of the nucleic acids in genetic phenomena, the genetic code, and the mechanism and control of the biosynthesis of proteins are three examples of the tremendous progress in this field. The entire second section of the present edition, therefore, deals with biochemical genetics and the role of nucleic acids and proteins in the process of transcription and translation of genetic information. Later sections are devoted to the chemistry and metabolism of cell constituents and of the various body tissues and fluids. Finally, the biochemistry of the nutrition of the living organism is considered. Thus the overall purpose is to correlate chemical subject matter with biologic processes in living matter. At the same time, every effort has been made to preserve proper consideration for the classic concepts of biochemistry and its relation to human problems as presented in earlier editions.

If preferred, the subject matter of the present edition is easily adaptable to the more traditional sequence of presentation. The chapters on the chemistry of the proteins, carbohydrates, and lipids (Chapters 5, 8, and 11) can be considered immediately after the introductory chapters (Section I), followed by those on metabolism, etc.

A number of chapters (1 through 7 and 14) have been completely rewritten because of extensive advances in these areas. Also, the other chapters have been partially rewritten and extensively revised to include important current developments. A number of new charts, tables, and illustrations have been added, and others have been deleted. Section V, on the vitamins and nutrition, has been almost completely redone.

Because of the vast expansion of biochemical literature during the past few years, increasing use of books, monographs, and reviews as general references at the end of each chapter has been made. The fewer special references to original papers in the literature are limited mainly to earlier classic papers describing original discoveries or concepts, or to current articles deemed of special significance. We offer regrets for any omission of important work not included because of space limitations or perhaps errors of human judgment.

Appendixes have been added to replace former text discussions dealing with physicochemical phenomena important in biochemistry and with newer techniques that have proved essential to recent progress in the field. The food tables of the Appendix of former editions have been discontinued, with references to other sources of this information being provided.

This edition has been designed with not only the needs of the medical student and students of other health-related sciences in mind but also those of the general biologist and chemist. Our hope is that it will prove of value to each.

The suggestions and comments, as well as assistance in other ways, of many colleagues and co-workers has greatly facilitated the preparation of this new edition. Special gratitude is due Dr. Ray K. Brown, for critically reading a number of chapters and making many helpful suggestions, and to Dr. Walter H. Seegers, who rewrote the entire section on the coagulation of blood. Deep appreciation is expressed to the following colleagues and friends for helpful suggestions and material: Drs. W. N. Arnold, G. J. Cox, Dana Dabich, Marilyn Doscher, M. F. Dunker, R. A. Hudson, A. C. Kuyper, R. A. Mitchell, F. C. Neuhaus, C. J. Parker, R. J. Peanasky, G. D. Small, E. H. Shaw, Jr., and S. N. Vinogradov. Gratitude is extended to fellow biochemists and journals who have generously permitted us to use illustrations, data, quotations, or concepts from their own publications. These have added greatly to the value of the book. Our thanks are also expressed to Louise Globke, Patricia Kosmyna, Maribel Andonian, and Evelyn Oden, for valued help in the preparation of the manuscript.

A special word of gratitude is reserved for our wives, for their constant support, aid, and understanding during the months required for the preparation of this manuscript. Dr. Aline U. Orten has read the final three chapters and offered many valuable suggestions and criticisms of these as well as of other chapters of the book. Special gratitude is also expressed to Dorothy E. Neuhaus for the preparation of numerous figures in Chapters 4 through 7 and 18 as well as for invaluable assistance in reading, organization, and correspondence.

Finally, and perhaps of greatest importance, gratitude is expressed to the users of this book. Their many helpful suggestions, comments, and criticisms have been invaluable in its continued revision and improvement. After all, the users of a book—postgraduate, graduate, and undergraduate students primarily, in this instance—are the *raison d'etre,* the very reason for its existence.

James M. Orten
Otto W. Neuhaus

CONTENTS

SECTION ONE

PREFATORY

1. BIOCHEMICAL CHARACTERISTICS OF LIVING MATTER, 3

Nature of biochemistry, 3
Development of biochemistry, 3
Chemical origin of living matter, 5
Biochemistry of living matter, 7

2. BIOCHEMICAL MORPHOLOGY OF THE CELL, 10

Cell membrane, 10
The nucleus, 16
The cytoplasm, 17

3. METABOLISM—AN OVERVIEW, 20

Definitions, 20
Specific enzymes and cofactors required, 20
Sequence of metabolic reactions, 21
Metabolic pathways, 21
Methods of study, 26

SECTION TWO

BIOCHEMICAL GENETICS
role of nucleic acids and proteins

4. STRUCTURE AND BIOSYNTHESIS OF NUCLEIC ACIDS, 29

Nucleoproteins, 30
Deoxyribonucleic acid, 37
Ribonucleic acid, 42
Biosynthesis of nucleic acids, 45
DNA and genetic information, 48
Semiconservative replication, 50
Genetic repair mechanisms, 52
In vitro replication of RNA, 52
Transcription of RNA, 53

5. AMINO ACIDS AND PROTEINS, 57

Amino acids, 58
Neutral amino acids, 58
Basic amino acids, 60
Acidic amino acids, 61
Imino acids, 62
Composition of proteins, 62
Stereoisomerism, 63
Solubility, 64
Isoelectric point, 65
Titration of amino acids, 65
Reactions of amino acids, 68
Peptide linkage, 70
Synthesis of peptides, 71
Primary structure, 74
Secondary structure, 77
Tertiary structure, 81
Quaternary structure, 83
Ionization, 87
Denaturation, 88

6. BIOSYNTHESIS OF PROTEIN translation of genetic information, 91

Genetic code, 91
Translation of genetic code, 94
Aggregation of subunits, 103
Control of protein synthesis, 103

7. BIOLOGICALLY ACTIVE PROTEINS the enzymes, 107

Early history of enzyme chemistry, 107
Protein structure and enzyme action, 108
Multienzyme systems, 131
Classification, 132
Clinical enzymology, 134

SECTION THREE

CHEMISTRY AND METABOLISM OF OTHER MAJOR CELL CONSTITUENTS

8. CHEMISTRY OF THE CARBOHYDRATES, 141

Definition, 141
Classification, 142
Monosaccharides, 143
Oligosaccharides, 162
Polysaccharides, 166

9. CARBOHYDRATE METABOLISM, 181

Digestion, 182
Absorption, 184
Hepatic interconversions of common monosaccharides, 185
General pathways of carbohydrate metabolism, 186
Glycogen storage diseases, 195
Utilization of glucose—glycolysis—Embden-Meyerhof pathway, 196
Metabolism of lactic acid and pyruvic acid, 203
Alternate pathways—pentose phosphate pathway (phosphogluconate shunt), 208
Carbohydrate metabolism in striated muscle, 211
Carbohydrate metabolism in heart muscle, 212

Carbohydrate metabolism in nervous tissue, 213
Conversion of carbohydrate to fat, 213
Excretion of glucose, 214
Metabolism of other hexoses, 214
Metabolism of pentoses, 216
Photosynthesis, 219
Abnormal carbohydrate metabolism, 221
Insulin, 224
Influence of other endocrine glands on carbohydrate metabolism, 233

10. BIOLOGIC OXIDATIONS, 237

Oxidations, 237
Respiratory enzymes and carriers, 242
Energy production and utilization—oxidative phosphorylation, 252
Degradation of carbon chains—decarboxylations, 262

11. CHEMISTRY OF LIPIDS, 269

Fats and oils—triglycerides, 270
Identification of fats and oils, 277
Essential fatty acids, 279
Waxes, 279
Sterols, 280
Phospholipids, 285
Glycolipids, 288
Lipoproteins and lipopolysaccharides, 290

12. LIPID METABOLISM, 292

Biochemical significance of fats, 292
Transport of fat, 298
Changes occurring in liver, 299
Fat from carbohydrates and proteins, 299
Fate of fats in body, 300
Oxidation of fatty acids, 305
Biosynthesis of fatty acids, 310
Synthesis of triglycerides, 314
Ketogenesis, 315
Common pathways of protein, carbohydrate, and fat metabolisms, 318
Essential fatty acids, 320
Metabolism of phospholipids, 321
Metabolism of glycolipids, 324
Metabolism of cholesterol, 325
Lipoproteins, 333

13. METABOLISM OF AMINO ACIDS, 338

Digestion of proteins, 338
Absorption of amino acids, 344
General paths of amino acids in the body, 345
Nitrogen balance, 346
Essential amino acids, 349
Urea formation, 359
Metabolism of some individual amino acids, 365
Creatine and creatinine, 395

14. METABOLISM OF NUCLEOTIDES AND PURINE AND PYRIMIDINE BASES, 400

Metabolic fate of nucleic acids, 400
Catabolism of purines, 401
Catabolism of pyrimidine, 402
Biosynthesis of purines, 403
Biosynthesis of pyrimidines, 407
Nucleoside triphosphates, 407

15. INORGANIC METABOLISM AND WATER BALANCE, 411

Inorganic composition of the body, 412
Water balance, 439

16. HORMONES, 453

Immunoassay of hormones, 454
Role of cyclic-AMP in hormone actions, 455
Hormones of the gastrointestinal tract, 456
Insulin, 458
Glucagon, 463
Epinephrine and norepinephrine, 464
Adrenocorticoids, 466
Cortisone and ACTH in rheumatoid arthritis, 475
Thyroid gland, 476
Parathyroid glands, 482
Pituitary gland, 484
Ovarian hormones, 498
Testicular hormones, 502

17. ENERGY METABOLISM, 512

Heat regulation of the body, 512
Respiratory quotient, 516
Basal metabolism, 520
Influence of muscular work on total metabolism, 532
Influence of mental work on total metabolism, 534
Influence of sleep, 534
Total heat production, 535
Metabolism of children, 535
Practical considerations, 535

SECTION FOUR

BIOCHEMISTRY OF SPECIALIZED TISSUES AND BODY FLUIDS

18. BIOCHEMISTRY OF SPECIALIZED TISSUES, 541

Biochemistry of malignant neoplasms (cancer), 567

19. BLOOD, 573

Blood plasma, 579
Erythrocytes, 594
Hemoglobin, 596
Leukocytes, 617
Platelets, 618
Blood coagulation, 619
Anemias, 634
Polycythemias, 636
Blood transfusion and blood substitution, 636
Blood pressure – vasoactive peptides, 638
Medicolegal tests for blood, 640

20. CHEMISTRY OF RESPIRATION AND ACID-BASE BALANCE, 643

Transport of oxygen, 645
Transport of carbon dioxide, 648
Acid-base balance, 654
Acidosis and alkalosis, 660

21. OTHER SPECIALIZED BODY FLUIDS AND SECRETIONS, 664

Secretions of gastrointestinal tract, 668
Saliva, 669
Gastric juice, 670
Pancreatic juice, 678
Intestinal juice – succus entericus, 679
Bile, 680
Liver function tests, 690
Chemical changes within the large intestine, 691
Milk, 699

22. URINE, 718

General characteristics, 720
General composition, 725
Abnormal constituents, 737
Detoxication, 747
Kidney function tests, 755

SECTION FIVE

NUTRITION

23. FAT-SOLUBLE VITAMINS, 761

Vitamin A, 765
Vitamin D, 777
Vitamin E – α-tocopherol, 786
Vitamin K, 789
Coenzyme-Q, 793
Antistiffness factor, 793
Summary, 794

24. WATER-SOLUBLE VITAMINS, 795

Ascorbic acid – vitamin C, 795
Thiamine – vitamin B_1, 802
Riboflavin, 806
Nicotinamide (niacin or niacinamide), 808
Pyridoxine, 811
Pantothenic acid, 814
Biotin, 817
Folic acid (pteroylglutamic acid, folacin), 819
Vitamin B_{12} (cobalamin), 823
Summary of water-soluble vitamins, 828
Other essential nutritional factors, 828
α-Lipoic acid, 834
Biosynthesis of vitamins, 834
Toxicity of the vitamins (hypervitaminosis), 834
Conditioned vitamin deficiencies, 835

25. NUTRITION, 837

Energy factor, 840
Protein factor, 843
Essential amino acids, 846

Carbohydrate factor, 855
Fat factor, 856
Mineral factor, 856
Acid-forming and base-forming properties of foods, 860
Vitamin factor, 861
Preservation of foods, 864
Diet therapy, 865

APPENDIXES

APPENDIX A
PHYSICOCHEMICAL PHENOMENA OF IMPORTANCE IN BIOCHEMISTRY, 879

Law of mass action, 879
Hydrogen ion and hydroxyl ion concentration, 880
Buffers, 883
Colloidal state, 888
Surface tension, 893
Diffusion, osmosis, and dialysis, 895
Viscosity, 900

APPENDIX B
ANALYTIC TECHNIQUES FREQUENTLY USED IN BIOCHEMISTRY, 901

Chromatography, 901
Ion-exchange chromatography, 902
Electrophoresis, 903
Ultracentrifugation, 903
Density gradient centrifugation, 904
X-ray diffraction, 904

SECTION **one**

PREFATORY

CHAPTER 1

BIOCHEMICAL CHARACTERISTICS OF LIVING MATTER

NATURE OF BIOCHEMISTRY

Biochemistry, according to a classic definition, is the study of the chemical composition of living matter and of the chemical changes that occur in it during life processes. In perhaps a broader sense, biochemistry may be defined as a discipline in which biologic phenomena are analyzed in terms of chemistry. Thus *biology*, including the medical and health sciences, poses the questions and, in this context, *chemistry* provides the intellectual and technical tools for their answer. Indeed, a working definition of a *biochemist*, adopted in 1965 by the American Society of Biological Chemists as a guideline for eligibility for membership in that society, is as follows: "A biochemist is an investigator who utilizes chemical, physical, or biological techniques to study the chemical nature and behavior of living matter."

Biochemistry, consequently, involves studies of the chemical constituents of the cell, the unit of living matter, and of the chemical mechanisms by which living material is formed, maintained, and eventually destroyed. The latter processes are conventionally termed *metabolism*. Hence, a major portion of biochemistry deals with this subject. The principal emphasis is properly on metabolism under normal, *physiologic*, conditions. However, deviations of metabolism under abnormal, *pathologic*, conditions will be considered too not only for so-called practical reasons but also because such deviations frequently aid in the elucidation of normal patterns. This will be evident as the subject is discussed in the ensuing pages.

DEVELOPMENT OF BIOCHEMISTRY

Biochemistry, as such, is a relatively young science, dating back only some 150 years. Indeed, the term *biochemistry* itself was not introduced until 1903 by the eminent German chemist Carl Neuberg. However, the beginnings of biochemistry date back much earlier than this and are intertwined with the development of the older sciences of organic chemistry (indeed of alchemy itself), physiology, biology, and medicine. The studies of the great Swedish chemist Karl Scheele, in the mid-1700's, on the chemical composition of plant and animal tissues contributed significantly to the founding of biochemistry as a separate discipline. Likewise, the classic investigations of Lavoisier (1785) on respiration, of Pasteur on fermentation, of Spallanzani, Reaumur, Beaumont, and Claude Bernard on digestion, and of Berzelius and Liebig in the first half of the 1800's on the quantitative analysis of naturally occurring substances served as a basis for later biochemical work and thought. Wöhler's chemical synthesis of urea in the 1820's permanently laid to rest the ancient belief that "vital forces" were required for the formation of biologically occurring organic compounds, thus placing biochemistry on a firm chemical foundation.

From these rather fragmentary beginnings, biochemistry emerged as a separate entity, sometimes termed "physiological chemistry" or "pathological chemistry," in the later 1800's. From this time into the early 1900's, high points in its development include Chevreul's pioneer work on the chemical nature of fats, Emil Fischer's classic studies on carbohydrates and amino acids, F. Miescher's discovery of the "nucleins" and nucleic acids, and E. Buchner's important observations on the fermentation of sugars by extracts of yeast, leading to the postulation of *enzymes* as organic catalysts.

The period of greatest progress in biochemistry, however, began in the 1920's with such classic investigations as those of Osborne and Mendel and of F. G. Hopkins on protein requirements for the animal organism; Hans Fischer's synthesis of heme; Funk, Mendel, and McCollum's pioneer discoveries on the vitamins; Sumner, Northrop, and Kunitz' studies on the chemical nature and functions of certain enzymes; and Harden and Young's and Embden and Meyerhof's work on the intermediary metabolism of carbohydrates. This period, into the 1930's, also included the brilliant discoveries of Steenbock, Elvehjem, and du Vigneaud in the vitamin field, and of Krebs, Szent-Györgyi, and others on the *citric acid cycle*, as well as W. C. Rose's now classic studies on the *essential amino acids*.

The post–World War II era witnessed the most remarkable period of progress in biochemistry. During this interval, and up to the present time, knowledge of the field has been estimated as *doubling every 8 years*, thus making biochemistry perhaps the most dynamic and productive area of human endeavor. This has been due to several fortunate occurrences in the early 1950's – the development of exquisitely sensitive and specific chromatographic methods for separating and identifying extremely small amounts of metabolites and other biologically active compounds, the availability of isotopes for "tagging" compounds and following their pathways in metabolism, and, of no less importance, the availability of sufficient funds for basic biochemical research. To illustrate the spectacular advances made in the past two decades, one needs only to mention such examples as the development of modern concepts of bioenergetics, the elucidation of the biosynthetic and degradative pathways for fatty acids, amino acids, and glucose, the details of the biosynthesis of cholesterol and certain steroid hormones and of heme, the determination of the primary, secondary, and tertiary structures of a number of biologically important proteins, and, of course, the elegant work on the structure of the nucleic acids with the concept of the role of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) in the genetic control of protein biosynthesis. A fuller discussion of these brilliant discoveries in modern biochemistry will make up a major portion of this book. It is safe to predict that the coming few decades will witness a similar, if not an even more dramatic, expansion of knowledge in this dynamic field.

CHEMICAL ORIGIN OF LIVING MATTER

> We living things are a late outgrowth of the metabolism of our Galaxy. The carbon that enters so importantly into our composition was cooked in the remote past in a dying star. From it at lower temperatures nitrogen and oxygen were formed. These, our indispensable elements, were spewed out into space in the exhalations of red giants and such stellar catastrophes as supernovae, there to be mixed with hydrogen, to form eventually the substance of the sun and planets, and ourselves. The waters of ancient seas set the pattern of ions in our blood. The ancient atmospheres molded our metabolism.
>
> *G. Wald*

This *vivid* statement expresses some of the highlights of current concepts of the chemical origin of living matter—a field that has developed significantly in the past few years. A somewhat more detailed proposition is that of Price,[1] summarized diagrammatically in Fig. 1-1. This scheme has been expressed similarly, in part at least, in a prevailing view that the chemical elements themselves *evolved* from nuclear reactions in stars, hydrogen being an early form of matter some 12 to 15 (or possibly even 70) billion years ago. Indeed, as Einstein once stated, "matter is energy congealed." From isotope-dating studies the age of the earth itself has been estimated as some 5 billion years.

There is now growing evidence to support the above concepts of the chemical origin of living matter. One of the fascinating developments in biochemistry during the past decade has been the beginning of some understanding of the origin of living matter from simple chemical molecules.

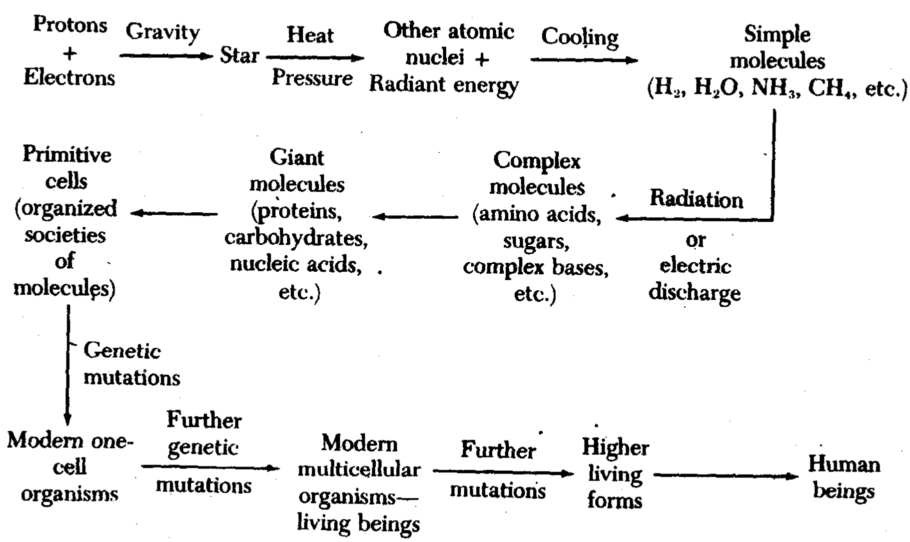

Fig. 1-1. Diagrammatic representation of the chemical origin of life. (From Price, C. C.: Sci. Res. 3:27, 1968.)

Primitive organic molecules such as hydrocyanic acid, acetic acid, formic acid, and formaldehyde began to be formed perhaps 3 to 4 billion years ago[2] from the primeval atmosphere composed of water, carbon dioxide, hydrogen, methane, and ammonia. The energy sources for these transformations were probably ultraviolet light from the sun, cosmic rays, and other types of radiation. Indeed, several scientists in the early 1950's found that the foregoing simple compounds, and even malic acid, aspartic acid, glycine, and alanine, could be formed in the laboratory from various mixtures of water, carbon dioxide, methane, ammonia, and hydrogen circulated past an energy source under conditions of temperature (150° C.) and pressure prevailing on earth at that time. More recently, methionine has been synthesized from ammonium thiocyanate in aqueous solution by ultraviolet irradiation under prebiotic conditions. Calvin and his co-workers[3] found that adenine can be formed from hydrocyanic acid under similar conditions. Other purine bases could have been formed from adenine, and pyrimidines undoubtedly could also have been produced similarly. Recent studies[4] have shown that the phosphorylation of one of the pyrimidine bases, uracil (as uridine), can occur in its aqueous solution under prebiotic conditions, with the resulting formation of 5′-uridine monophosphate (UMP), a constituent of nucleic acids. Ribose and other sugars could have arisen from the polymerization of formaldehyde. Likewise, the polymerization of amino acids into *proteinoids* has been accomplished by heating (180° to 200° C.) amino acid mixtures in nitrogen gas.[5] These proteinoids have many properties of typical proteins. Glycogen, starch, and perhaps other important polymers could also be formed by a similar *abiologic* process. Several amino acids have been identified in fossil dinosaur bones and clam shells 150 to 300 million years old.[6] Currently,[7] some 22 different amino acids have been identified in a sample of pre-Cambrian sedimentary rock that is at least 3.1 billion years old.

Thus, under primeval conditions, it has been possible to produce and identify the preformed "building stones" (monomers) of living matter—i.e., the sugars, fatty acids, and amino acids, as well as their polymers, the proteins, lipids, and starch and glycogen, and the purine and pyrimidine bases that are essential constituents of nucleic acids. The latter, as will be seen, form the transmissible "code" for the synthesis of protein and other essential constituents of living matter.

Undoubtedly, catalysts for the regulation of the preceding synthetic processes must have been necessary then as now. Enzymes, an important class of biocatalysts, could have evolved from the proteinoids just mentioned. It is interesting that porphyrin derivatives, which are present in a number of biocatalysts, have been synthesized by several groups of investigators[8] under simulated primordial conditions, using a mixture of ammonia, methane, and water through which was passed a 12,000-volt continuous electric arc between tungsten electrodes. Porphyrins also showed up quite early in the evolutionary scheme. A recent report[9] states that porphyrins have been found in microfossils dated about a billion years ago. Likewise, Margoliash and Smith[10] have estimated that the cytochrome molecule has existed some 2 billion years! Since that time, cytochrome-c, like the hemoglobin molecule and a number of other functionally important proteins (e.g., certain enzymes), has undergone chemical evolutionary changes, in terms of portions of its amino acid sequence, that parallel the biologic evolution of the various animal species. Undoubtedly, preceding changes occurred in the base sequence of DNA, which controls by way of the several types of RNA the biosynthesis of these proteins in vivo.[11]

With the chemical evolution of the porphyrin molecule, the synthesis of chlorophyl by plants became possible; and, in turn, with the cytochromes and necessary cofactors (vitamin K–like substances), the generation by *cyclic phosphorylation* of chemical energy (adenosine triphosphate, ATP) from light energy of the sun was made possible. Such chemical energy then became available for the photosynthesis of carbohydrates from carbon dioxide and water, and for other biosynthetic reactions.[12] Thus, current evidence indicates that photosynthetic organisms with suitable catalysts have existed for more than a billion years, affording conditions that would complete the requisites for the synthesis of living matter from simple organic compounds even at this early period of biochemical evolution. Of course, it is also possible that some living matter may have been derived from meteorites from outer space, as postulated in the "seeding" theory.

BIOCHEMISTRY OF LIVING MATTER

Living matter, or protoplasm, cannot be defined adequately. It differs from lifeless material in possessing the capabilities of growth, repair, and reproduction. These properties may not be apparent at all times in the same degree, but they are present to some extent in all living organisms. Moreover, the life processes go on at comparatively low temperature and with great rapidity, the synthesis of a complex protein molecule such as hemoglobin, for example, apparently requiring only a few seconds. Comparable reactions in the laboratory, even if possible, require high temperatures, often with increased pressure, or else they go on very slowly and quite incompletely. Many reactions of the living cell are of great complexity – intricate interwoven oxidations, disintegrations, and syntheses – in comparison with which the manifold simultaneous operations of an electronic computer are like simple mechanical toys. Some of these marvelous reactions are known and partly understood. Many others are appreciated only because of our awareness of the end products. We must be impressed by the orderly way in which all the chemical activities of the body coordinate. This may be another attribute of living matter, the orderliness of its chemical reactions.

Chemical composition

Protoplasm is composed of water, inorganic salts, and organic compounds. Water is a most important compound in tissues and comprises some 75% to 85% of the weight of most cells. The water of the tissues and body fluids is mostly in the free state; i.e., substances may be dissolved in it and it may pass back and forth from blood to tissues, in and out of cells. A small fraction of the water is believed to be bound. In other words, some of the water in hydrophilic colloid systems is combined so that the activity of the water molecules is reduced considerably. Free water varies according to diet and physiologic activity, whereas bound water is a rather constant constituent of the tissues.

Recent studies[13] using deuterated water (D_2O) in dogs have shown that the average water content of the body as a whole is 61% of body weight, with a range of 55% to 67%. The water content of the human body apparently has about the same range, being less than average in fat individuals and somewhat greater in thin persons. The water content of individual tissues also varies considerably, as will be discussed later.

Water content

There are several mechanisms for maintaining and controlling the water content of the tissues (Chapter 15). When these go wrong, a number of pathologic states may ensue. Dehydration is a condition not at all uncommon and is likely to have a fatal outcome if not recognized and combatted. Edema is another—a condition in which fluid leaves the bloodstream and accumulates in the tissues. Sometimes what appears to be a minor disturbance results in a major catastrophe.

Water is needed for many and varied reasons. It is the solvent, the agency that enables water-soluble, water-miscible, or emulsifiable substances to be transferred in the body, not only in the blood, which is more than four-fifths water, but also intercellularly and intracellularly. Ionization takes place in water, and ionization is a prerequisite to many biochemical reactions.

In the regulation of body heat, water is most important because of its peculiar physical properties. It possesses *high specific heat;* i.e., the amount of heat required to raise the temperature of a gram of water 1° C. is much higher than the amount of heat required to raise the temperature of a gram of some other substance 1° C. The specific heat of water is 1. The values for all other common substances are much smaller. This enables the body to store heat effectively without greatly raising its temperature. Water has *high heat conductivity*. This permits heat to be transferred readily from the interior of the body to the surface. Finally, water possesses *high latent heat of evaporation*, which causes a great deal of heat to be used in its evaporation and thus cools the surface of the body. These are physical properties useful to the body in the physiologic regulation of body temperature.

Inorganic and organic constituents

At least 60 of the 102 or more elements believed to be present in the universe occur in biologic matter. Only some 20 to 22 of these are found consistently, however, and some are present only in extremely minute amounts. About 1% of the total weight of an average soft tissue is ash, or inorganic salts, chiefly of the cations Na^+, K^+, Mg^{++}, Ca^{++}, NH_4^+ and the anions Cl^-, $H_2PO_4^-$, $HPO_4^=$, HCO_3^-, $SO_4^=$. Some of these may be linked to organic radicals, as is also the case for Fe, I, Cu, Zn, and Mn. Other *trace elements* consistently found in nearly all forms of living matter include B, Cr, Co, F, and Si. Biochemical functions of Co, F, and probably Cr, are now known, as will be discussed later (Chapter 15). Other elements are found in small amounts in some species, but as yet no definite function for them has been established. These include Ag, Al, As, Ba, Be, Br, Cd, Cs, Ge, Li, Mo, Ni, Pb, Rb, Se, Sn, Sr, Ti, and V. A few other elements, which are regarded as contaminants or accidental constituents, may be found in living matter. These include Ar, Au, Bi, He, Hg, and Tl.